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DESCENDING PATHWAYS FROM THE BRAIN STEM TO THE SPINAL CORD IN SOME REPTILES

H.J. TEN DONKELAAR

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Promotor: Prof. Dr. R. Nieuwenhuys

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" If the highly variable modes of propulsion characterizing individual species be considered, fundamental variations in the organization of the central motor apparatus seem almost certain to exist, but it cannot be predicted whether such differences will be found to have their major anatomical expression at the level of the lower motor system, at higher levels, or in the disposition of descending conduction systems".

Nauta and Karten, '70.

Voor Jiřina en Mischa

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CONTENTS

I INTRODUCTION

From normal anatomical descriptions (cf. Ariëns Kappers et al., '36; Nieuwenhuys, '64) as well as from sparse experimental studies (Robinson, '69; W. Cruce, '74) it appears likely that the fibre systems descending from the brain stem to the spinal cord in reptiles, are largely comparable to those of mammals.

The descending fibre paths to the spinal cord in mammals have been grouped by Kuypers (Kuypers et al., '62; Kuypers, '64; Lawrence and Kuypers, '68a, b) into two functional systems, which he termed the medial and the lateral system. The medial system comprises the reticulospinal, vestibulospinal and interstitiospinal tracts and descends chiefly via the funiculus ventralis. The lateral system consists of the corticospinal and rubrospinal tracts and descends by way of the posterolateral funiculus. The medial system of descending paths to the spinal cord influences mainly motoneurons innervating trunk and proximal extremity musculature, whereas the lateral system is more particularly related via interneurons to the motoneurons innervating the distal muscles of the extremities.

The corticospinal tract in higher primates is characterized by the presence of direct connexions to the motoneurons innervating the distal muscles of the extremities. This has been regarded as a high level of phylogeny. However, evidence has been gathered that other animals which are very definitely not primates, but which have very detailed finger movements like the raccoon, likewise have such direct connexions from the motor cortex to the motoneurons in question (Petras, '68, '69; Wirth et al., '74). This emphasizes the point that some structural features which have been looked upon as being a phylogenetic development, in reality are concerned with a type of motor performance (Kuypers, discussion in Nieuwenhuys, '64).

It should be stated beforehand that in reptiles there is no evidence for the presence of a direct projection from the telencephalon to the spinal cord (Lohman and Mentink, '72; Lohman et al., '73; Hall and Ebner, '74; Hoogland, '75). However, a well developed red nucleus is present in reptiles (de Lange, '12;

Beccari, '23).

The aim of the present study is to analyse the fibre systems descending to the spinal cord in some reptiles. With regard to their mode of progression reptiles can be roughly divided into the following three groups: a) those using for their locomotion solely trunk musculature: limbless lizards and snakes; b) reptiles, moving by way of trunk musculature as well as by way of their extremities: lizards and crocodiles; and c) a group employing only their extremities: chameleons and turtles.

For the present inquiry of each of these three groups one representative was chosen, viz., the snake Python reticulatus, the lizard Tupinambis nigropunctatus and the turtle Testudo hermanni.

As a preliminary step it was felt necessary to make an analysis of normal material, more in particular of series stained according to Nissl and Häggqvist ('36). The latter technique, a modification of the Alzheimer Mann methylblue-eosin technique, was introduced in Holland by Verhaart and his school, and has been used so far only in mammals (van Beusekom, '55; Busch, '61; Verhaart, '70) and in the pigeon (Zecha, '61; van den Akker, '69, '70). Its chief advantage over more classical methods is that it shows both the axon and the myelin-sheath of each separate fibre in contrasting colours. In Häggqvist material many bundles and tracts can be clearly distinguished from their environment on account of their characteristic fibre pattern, i.e. the calibre spectrum of their constituent fibres (van Beusekom, '55). The descending fibre systems to the cord stand out conspicuously in the brain stem because of their high contingent of coarse fibres.

In chapter III this analysis of normal material is presented. For a better understanding of the fibre systems in question an atlas has been made based on series stained according to Nissl and Häggqvist.

Before presenting the experimental results a short description of the spinal cord is given in chapter IV.

For the experimental verification of the fibre systems recognized

in the analysis of normal material various techniques have been used. The first part of the experimental work (presented in chapter V) concerns the exact origin of the descending supraspinal fibre systems. The following procedures have been used: 1) recording the occurrence of retrograde cell changes following spinal cord hemisections, and 2) searching for labeled cells following injection into the spinal cord of the enzyme horseradish peroxidase, a protein which is transported retrogradely in the axon (Kristensson et al., '71; LaVail and LaVail, '72; LaVail et al., '73).

The second part (chapter VI) deals with the course and site of termination of the fibre systems demonstrated in the Häggqvist material, viz., rubrospinal, vestibulospinal, reticulospinal and interstitiospinal tracts. Lesions have been placed in the brain stem and the ensuing fibre degeneration has been traced with anterograde degeneration techniques (Nauta and Gygax, '54; Fink and Heimer, '67).

In the general discussion (chapter VII) a comparison of the descending fibre systems to the spinal cord is made first among the reptiles studied, and second with other classes of terrestrial vertebrates, viz., with amphibians (Corvaja and Grofová, '72; Corvaja et al., '73) with the pigeon (van den Akker, '69, '70) and with mammals. Particularly in the opossum (Martin, '69; Martin and Dom, '70a, '71; Martin et al., '74), the cat (Staal, '61; Nyberg-Hansen, '66) and in the monkey (Kuypers et al., '62; Lawrence and Kuypers, '68a, b) extensive studies have recently been made concerning the fibre systems in question.

II MATERIALS AND TECHNIQUES

For the description of the nuclear masses in the brain stem transverse series of the brains of each reptile studied were used stained with cresylechtviolet. The analysis of the fibre systems is based on series stained according to Häggqvist's ('36) modification of the Alzheimer Mann methylblue-eosin stain. Further material for reference included series stained according to Klüver and Barrera ('53).

For the experimental part of this study altogether 40 turtles (10 Pseudemys scripta elegans and 30 Testudo hermanni), varying in weight from 200 to 1050 grams, with a carapace length of 11,5 to 14 cm, 18 snakes (Python reticulatus), 575 to 1500 grams with a snout-vent length of 106 to 122 cm, and 58 lizards (Tupinambis nigropunctatus), varying in weight from 700-3200 grams, with a total length of 70-98 cm and a snout-vent length of 28-34 cm.

All experiments were carried out under surgical anesthesia. Initially the turtles were anesthesized with Nembutal (20-30 mg/kg body weight, a 30% solution in physiological saline) administered intraperitoneally. This anesthesia appeared to be rather unreliable, hence in later experiments the turtles were intubated and received endotracheal anesthesia for which a mixture of 0.5 l O_2, 50-100 ml N_2O with ¼-½ volumen-% halothane was employed. This technique showed to be very safe (cf. Kaplan, '69; Calderwood, '71; Lumb and Jones, '73). The Pythons also received Nembutal-anesthesia, administered in doses of 20-25 mg/kg body weight (dissolved in physiological saline) into the caudal third of the coelomic cavity. Surgical anesthesia was reached on the average in 60 minutes and persisted for at least 3 hours. The lizards (Tupinambis nigropunctatus) were anesthesized with Nembutal, injected into a large vein at the inferior surface of the tongue in doses of 20-24 mg/kg body weight (a 30% solution in physiological saline) as described by Lohman and Mentink ('72). With this technique surgical anesthesia is reached in a few minutes and persists for at least 5 hours.

The operations were carried out under sterile conditions (except for the turtle, where this is hardly necessary) with the aid of a Zeiss binocular operation microscope. The following techniques have been used:

1) spinal hemisections: following a midline skin incision and separation of the bilateral dorsal musculature laminectomy was performed. The dura was incised and a complete or partial hemisection was performed with a von Graefe cataract knife. These operations were carried out at various levels of the spinal cord.
2) injection of the enzyme horseradish peroxidase (HRP). This technique was adopted from Kristensson et al. ('71), LaVail and LaVail ('72), and LaVail et al. ('73). Following laminectomy and incision of the dura, the enzyme HRP (type VI, Sigma) was injected under direct vision into the spinal cord (cervical and lumbar intumescences) of the turtle Testudo hermanni and the lizard Tupinambis nigropunctatus. The enzyme was dissolved in physiological saline in a concentration of 200 µgm per µl and was administered in a dosis of 0.5 µl through a 26 gauge needle from a Hamilton syringe in portions of 0.1-0.2 µl over a period of 10-20 minutes.
3) lesions in the brain stem: following a midline skin incision and spreading of the temporal muscles a hole was drilled in the skull. After having incised the meninges, a lesion was made either by a surgical approach (tectum and vestibular area) or electrolytically by delivering a current of 1 mA for 10 seconds through an etched steel electrode insulated up to 0.2 mm from the tip (red nucleus and reticular formation).

Following surgery, the animals were kept at an environmental temperature ranging from 24 to 27°C (the snakes 27-30°C) and sacrificed after postoperative survival times of 2 to 7 days for the reptiles in which HRP was injected into the cord, and 10-90 days for the other experiments. The reptiles used in the latter experiments (i.e. the spinal hemisections and the lesions in the brain stem) were perfused

through the heart under deep Nembutal anesthesia, with physiological saline, followed by 10% formalin (in a few cases for the retrograde studies Heidenhain's Susa mixture has been used, which showed not to be advantageous over formalin). After their removal the brain and spinal cord were further fixed in 10% formalin for periods varying from 2 to 10 weeks, The brains which were used to study the retrograde cell changes following spinal cord lesions were embedded in paraffin, cut transversally at a thickness of 15 micra and stained with cresylechtviolet. The part of the spinal cord containing the lesion was treated in the same way, but stained with the hematoxylin-eosin technique.

The material obtained from the lesions in the brain stem was, in order to study the ensuing anterograde degeneration, embedded in albumin, sectioned transversally on a freezing microtome at 25 μm thickness and subsequently stained with the Nauta-Gygax ('54) and Fink-Heimer ('67) techniques.

The brains and spinal cords of the animals in which HRP was injected into the spinal cord, were processed as follows.
These reptiles were perfused through the heart after survival times of 48 hours to 7 days with a mixture of 1% formaldehyde and 1.25% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4). The brain and the part of the spinal cord in which the enzyme has been injected were removed and stored overnight in the refrigerator in phosphate buffer containing 5% sucrose. The material was then frozen in dry ice and cut into sections of 40 μm in the transversal plane on a freezing microtome. The sections were incubated in a medium containg hydrogen peroxide and 3.'3 - diaminobenzidine tetrahydrochloride in tris-HCL buffer (pH 7.6) for 10 minutes at room temperature, and mounted in Entellan. Part of the sections was counterstained with cresylechtviolet.

III THE PATHWAYS DESCENDING FROM THE BRAIN STEM TO THE SPINAL CORD AND THEIR CENTRES OF ORIGIN

A preliminary reconnaissance, based on normal Nissl and Häggqvist material.

The brain stem as defined here comprises the mesencephalon and the rhombencephalon. It contains the nuclei of origin and termination of most cranial nerves. In addition the brain stem of reptiles contains a well developed reticular formation and numerous sensory and motor relay nuclei, as e.g. a red nucleus, with their associated ascending and descending connexions.

A short description of the areas expected to give rise to descending systems to the spinal cord, based on a survey of the reptilian brain stem (ten Donkelaar and Nieuwenhuys, '75), will be given here. The following centres will be discussed: 1) the tectum mesencephali, 2) the red nucleus, 3) the vestibular nuclear complex and 4) the reticular formation.

In order to show the topographical relationships of the various cell masses and fibre systems described, cross sections through consecutive levels of the brain stem and through the first spinal segment of the species studied are represented in figures 1-34. These figures show the cell picture at the left and the fibre systems at the right. For the representation of the latter dots of three different sizes are employed. The general terms small, medium-sized and coarse fibres are used to describe the fibre pattern of the various systems. These sizes are not strictly defined, but in general it may be said that the small fibres range from 0 to 3 µm, the medium-sized ones from 3 to 6 µm, and the coarse fibres from 6 to 12 µm.

The tectum mesencephali

In reptiles the tectum mesencephali receives the bulk of the fibres of the optic nerve. In addition to this visual input the tectum has been reported to receive fibres from several other sources, i.e. from the lateral lemniscus, from trigeminal centres and from the spinal cord. On account of this diversity of input the tectum has been considered as a correlation centre.

The large well developed tectum mesencephali of reptiles is characterized by its subdivision into a number of highly differentiated layers. Ramón (1896, Chameleon) distinguished fourteen layers. Huber and Crosby ('26, '33; various reptiles) were of the opinion that several of the layers described by Ramón can be considered substrata of one and the same zone. So they arrived at a subdivision into the following six layers:

1) the stratum opticum, the outer layer, receiving the fibres from the optic tract;

2) the stratum fibrosum et griseum superficiale, considered as a receptive and correlative layer;

3) the stratum griseum centrale, consisting of neurons, the axons of which constitute a most important part of the efferent system of the tectum;

4) the stratum album centrale, in which many of the axons of the previous layer descend;

5) the stratum griseum periventriculare. The short dendrites of this periventricular gray extend toward the ventricle to come into relation with entering fibres of the diencephalic and mesencephalic periventricular system (Huber and Crosby, '26, '33).

6) the stratum fibrosum periventriculare, which constitutes the innermost layer of the tectum.

This subdivision into six layers is employed by most present-day workers. In the species used for the present study they could be clearly distinguished (figs. 1-3, 12-14), except for the Python, where a more diffuse arrangement was found (cf. figs. 24-26).

The efferent connexions of the tectum mesencephali can be divided into an ascending and a descending projection. Recent experimental studies (Ebbesson, '70a; Hall and Ebner, '70a; Butler and Northcutt, '71; Braford, '72; Foster et al., '73) have demonstrated that the ascending projection of the tectum terminates mainly in the nucleus rotundus, a centre situated in the dorsal thalamus. Some fibres of this tectothalamic tract end in the ventral part of the lateral geniculate nucleus and in certain pretectal nuclei, whereas a crossed

component reaches via the supraoptical commissure the contralateral nucleus rotundus and the nucleus geniculatus lateralis, pars ventralis. For a description of the normal anatomy of the reptilian diencephalon reference is made to the studies of Papez ('35, Chelone midas), Senn ('68, Lacerta sicula), Butler and Northcutt ('73, Iguana iguana), and J. Cruce ('74, Tupinambis).

The descending projections of the tectum mesencephali have been divided into dorsal, intermediate and ventral (or lateral) tectobulbar tracts (de Lange, '10, '13). The dorsal tract, i.e. the tractus tectobulbaris dorsalis, crosses the midline just ventral to the fasciculus longitudinalis medialis (f.l.m.) and continues caudalward as the fasciculus predorsalis. In our Häggqvist material this bundle extends throughout the rhombencephalon, in which it is situated immediately ventral to the f.l.m.

In the literature (de Lange, '10, '13; Papez, '29; Leghissa, '54) the presence of a tectospinal component of the predorsal bundle has been suggested. In the Häggqvist material at our disposal no tectospinal tract could be demonstrated. However, that the tectum mesencephali exerts motor influence over the spinal motor apparatus, has been shown by stimulation experiments in Caiman (Bagley and Langworthy, '26; ten Cate, '37; Goodman and Simpson, '60; Shapiro and Goodman, '69), e.g. tilting of the head was noted. These authors do not state whether these effects are direct or indirect, i.e. via the reticular formation.

The intermediate tectobulbar tract chiefly termiantes in the ipsilateral tegmentum mesencephali. The ventral tectobulbar tract descends along the ventrolateral border of the rhombencephalon. In the Häggqvist material this tract could not be traced as far caudally as the predorsal bundle.

The red nucleus

The nucleus ruber (figs. 3, 13, 25) is rather well developed in most reptiles (de Lange, '12; Beccari, '23; Shanklin, '30; Frederikse, '31; Senn, '68). In the snake Python reticulatus the nucleus in question can hardly be distinguished (cf. fig. 25). The nucleus ruber

consists of medium-sized and large cells, the latter situated in the caudal part of this nucleus.

In reptiles a brachium conjunctivum takes its origin from the lateral cerebellar nucleus and terminates in the contralateral red nucleus (Shanklin, '30; Larsell, '32). This tract could be distinguished in the Häggqvist material as a thin-fibred system (cf. e.g. figs. 14-16). An extension of the brachium conjunctivum to thalamic levels is not known, and experimental data are entirely lacking.

With regard to the efferents of the red nucleus a tractus rubrospinalis has been described by previous workers (de Lange, '12; Papez, '29, '35). In the Häggqvist material of the lizard Tupinambis nigropunctatus and also of Caiman (cf. ten Donkelaar and Nieuwenhuys, '75) this system stands out as a bundle of medium-sized fibres, occupying a position comparable to that in the pigeon (Zecha, '61; van den Akker, '69, '70) and in the opossum (Martin and Dom, '70a). Just caudal to the red nucleus these medium-sized fibres cross the midline, move into a dorsal direction along the periphery of the tegmentum mesencephali and take a position directly ventromedial to the descending tract of the trigeminal nerve (cf. figs. 14-19). At caudal levels of the brain stem (figs. 20-21) the rubrospinal tract shifts dorsally from its lateral position and finally takes a position in the most dorsal part of the lateral funiculus of the spinal cord (cf. fig. 22). In the Häggqvist material of the turtle and the snake the presence of a rubrospinal tract could not be demonstrated. Robinson ('69) has experimentally confirmed a rubrospinal projection in the lizard Lacerta viridis.

The vestibular nuclear complex

The vestibular nuclei in reptiles have been extensively studied by Weston ('36). He distinguished six vestibular nuclei: the nucleus vestibularis ventrolateralis, - tangentialis, - ventromedialis, - descendens, - dorsolateralis and - superior. This subdivision of the vestibular nuclear complex is also used in the present study.

The nucleus vestibularis ventrolateralis (Vevl, figs. 7, 18, 19,

29 and 30) consists of very large cells, among which small elements are scattered. It is particularly well developed in the lizard. This nucleus is considered as the equivalent of the mammalian nucleus of Deiters (de Lange, '17; Weston, '36).

The nucleus vestibularis tangentialis (Vetg, figs. 7, 8, 18, 19, 29, 30) consists of a collection of medium-sized cells, intercalated among the entering fibres of the vestibular root. It is situated directly lateral to the nucleus vestibularis ventrolateralis. Weston ('36) and Stefanelli ('44a, b) have suggested that the degree of development of the tangential nucleus is correlated with the relative development of the trunk musculature.

The nucleus vestibularis ventromedialis (Vevm, figs. 7, 8, 18-20, 29, 30) is a rather ill-defined cell mass, consisting of medium-sized cells. It is situated in the ventrolateral angle of the fourth ventricle and extends along the whole length of the vestibular region.

The nucleus vestibularis descendens (Veds, figs, 8, 20, 30), which can be considered as the more diffuse, caudal continuation of the ventrolateral vestibular nucleus, has also been termed the inferior nucleus (Beccari, '11; Stefanelli, '44a). It consists of medium-sized and small cells. Its most caudal part merges with the dorsal funicular nucleus.

The nucleus vestibularis dorsolateralis (Vedl, figs. 6, 17, 28) has also been called the nucleus superior by various authors (e.g. Beccari, '11; Papez, '29 and Stefanelli, '44a). It is situated between the ventrolateral vestibular nucleus and the deep cerebellar nuclei. The boundaries of this rather diffuse nucleus are ill-defined.

The nucleus vestibularis superior (Ves, fig. 5) has been considered by Stefanelli ('44a) as a direct rostral continuation of the medial part of the dorsolateral vestibular nucleus. It is situated between the nucleus cerebelli lateralis and the nucleus princeps n. trigemini from which it is very poorly delimited. So far this cell mass has only been distinguished in the turtle.

Stefanelli ('44a, b) remarked upon considerable differences in the development of the vestibular nuclei and their connexions. The ventro-

lateral and dorsolateral nuclei are strongly developed in reptilian forms with a wholly or partly quadruped locomotion, whereas in species with a purely serpentine mode of progression, the nucleus tangentialis is particularly large. The observations made in the present study concur with the results of Stefanelli.

Apart from afferents entering via the vestibular nerve, the vestibular nuclear complex receives afferents from a variety of sources, viz., from the spinal cord, from the cerebellum and from some cranial nerve nuclei (Weston, '36). Leake ('74, Caiman) and deFina and Webster ('74, Tupinambis) recently demonstrated with experimental techniques the projection from the vestibular nerve to the various nuclei of the vestibular complex.

A small spinovestibular projection has been demonstrated by Ebbesson ('67, '69). These fibres ascend with those of the dorsal spinocerebellar tract and terminate in the ventral part of the ventrolateral vestibular nucleus. In addition some fibres were shown to end in the ventromedial nucleus. After midthoracic or more caudal lesions only very few fibres could be traced to the vestibular nuclear complex. In mammals however, it is known that spinovestibular fibres originate mainly, although not exclusively from the lumbosacral levels of the spinal cord (Pompeiano and Brodal, '57b).

As regards the efferent connexions of the vestibular nuclear complex, projections to the cerebellum, the brain stem and the spinal cord have been described.

Connexions of the vestibular nuclear complex with the brain stem, in particular with the nuclei which supply the external eye muscles (III, IV and VI) have been described by Beccari ('11), Weston ('36) and Stefanelli ('44a, b). These fibres were supposed to pass via the fasciculus longitudinalis medialis (f.l.m.), which tract will be discussed in the section devoted to the reticular formation. The presence of such a vestibulomesencephalic connexion, passing via the f.l.m. is strongly suggested in the Häggqvist material.

On the basis of the Häggqvist material the vestibulospinal fibres constitute two bundles, the tractus vestibulospinalis lateralis and

the tractus vestibulospinalis medialis, the fibres of the latter enter the f.l.m. The tractus vestibulospinalis lateralis, the better developed of the two, arises from the ventrolateral vestibular nucleus. It can be traced as a bundle of coarse fibres descending through the lower brain stem. During its course through the caudal rhombencephalon it gradually shifts ventromedialward, attaining finally a superficial position, just lateral to the f.l.m. (cf. e.g. figs. 18-22). The lateral vestibulospinal tract is particularly well developed in the lizard, but rather small in the snake. The existence of a direct projection from the ventrolateral vestibular nucleus to the spinal cord has been experimentally shown by Robinson ('69) in the lizard Lacerta viridis. After spinal hemisection this author found an appreciable chromatolysis in the neurons of the ventrolateral nucleus, particularly in the ipsilateral one.

The reticular formation

The reticular formation of reptiles shows an evident resemblance to that of mammals. As has been done by Brodal ('57) for the cat, the reticular formation in reptiles can be subdivided into three longitudinal zones, median, medial and lateral (Cruce and Nieuwenhuys, '74; ten ten Donkelaar and Nieuwenhuys, '75). The medial zone is confined to the rhombencephalon and consists of cells situated in or near the raphe, forming two condensations, the nucleus raphes inferior and the nucleus raphes superior. The nucleus raphes inferior consists of large elements, whereas the nucleus raphes superior is built up of small cells. The medial column contains the magnocellular reticular nuclei, and in addition, certain mesencephalic centres. The lateral reticular zone, a large diffuse area which consists of small cells, is situated throughout its extent directly medial to the descending nucleus of V. Cruce and Nieuwenhuys ('74) considered it quite possible that this area contains the primordium of the 'lateral reticular formation' of mammals. Yet a further subdivision of it on a cytoarchitectonic basis appeared to be impossible.

The Golgi-studies of Newman ('74, '75) indicate that the reptilian reticular formation is composed of neurons which as regards their

dendritic ramification pattern can be qualified as isodendritic (cf. Ramón-Moliner and Nauta, '66). The latter authors demonstrated that in mammals the reticular formation is mainly composed of neurons with long, poorly ramified dendrites, for which the term isodendritic neurons was suggested. The latter neurons represent a pool of pluripotential neurons which in the course of phylogeny have remained relatively undifferentiated (Ramón-Moliner and Nauta, '66; Nauta and Karten, '70).

The medial reticular zone consists of a series of nuclei which together constitute an almost continuous chain, extending throughout the brain stem. Ariëns Kappers et al. ('36) introduced a number of simple and clear terms for the principal magnocellular rhombencephalic centres of this zone, viz., the nucleus reticularis inferior, - medius and - superior. These nuclei contain besides the large elements also small scattered cells (Cruce and Nieuwenhuys, '74). The subdivision mentioned above has been made based on the clustering of the large elements, as already indicated by van Hoëvell ('11).

In topographical reconstructions in a horizontal plane of each of the three species studied (figs. 11,23,34) the large elements have been indicated to give an impression of their distribution and density. In these figures in order to reduce crowding about one out of five cells have been marked. These reconstructions revealed that some considerable variation exists among the species studied. The median and medial magnocellular zone are particularly large in the snake, which led Stefanelli ('41) to the conclusion that the nuclei in question are functionally related to the control of the trunk musculature.

The most rostral part of the rhombencephalic reticular formation is constituted by a somewhat ill-defined cell mass, which has been termed, in accordance with Stefanelli ('41, '44a) the nucleus reticularis isthmi. Rostral to this cell mass the mesencephalic reticular formation is found, in which, rostral to the red nucleus, the large-celled nucleus interstitialis of the f.l.m. is situated.

The fibre connexions of the reptilian reticular formation are imperfectly known. Afferents to the reticular formation have been experimen-

tally demonstrated from the spinal cord (Ebbesson, '67, '69; Pedersen, '73), and from the tectum mesencephali (Foster et al., '73).

Many efferent fibres of the reptilian reticular formation appear to enter the fasciculus longitudinalis medialis (f.l.m.). Prior to the discussion of this contribution to the f.l.m. some general notes on this bundle have to be made.

The fasciculus longitudinalis medialis is a rather complex bundle, which received much attention in the older literature (Ramón, 1897; Edinger, 1899; Beccari, '22, '23; Tuge, '32; Stefanelli, '44a; Leghissa, '54). It extends from the interstitial nucleus of the f.l.m., which as its name implies contributes to it, and extends throughout the brain stem, continuing caudally into the ventral funiculus of the spinal cord as the sulcomarginal fasciculus. In the brain stem the f.l.m. is situated just lateral to the median plane, showing a close relation to the somatic motor nuclei. In our Häggqvist material the f.l.m. stands out as chiefly composed of coarse fibres. The bulk of its constituent fibres arises from the vestibular nuclear area and from the medial reticular zone. The ascending and descending fibres from the vestibular area contributing to the f.l.m. have already been discussed. The magnocellular reticular nuclei send fibres by way of the bundle in question to the spinal cord. In favourable Häggqvist sections axons of reticular cells can be traced over considerable distance into the direction of the f.l.m. (cf. e.g. figs. 16-18). At the level of the nucleus reticularis medius these fibres constitute a separate lateral bundle (fig. 18), which at a more caudal level becomes incorporated into the f.l.m. Because of the many entering reticulospinal fibres the f.l.m. increases in size caudalward.

The nucleus reticularis inferior sends its axons in addition to the spinal cord via the lateral funiculus.

A few notes on the problems in studying the reticulospinal pathways may be appropriate here. Because of the diffuse arrangement of the cells in the reticular formation it can be expected that lesions (electrolytically or surgically made) within its confines would destroy fibres of many different sources. On this account the most reliable anatomical

approach for determining the origin of reticulospinal fibres is to study the ensuing retrograde cell changes following lesions of the spinal cord.

Conclusions:

The analysis of Häggqvist preparations suggests that in reptiles the following fibre systems descend from the brain stem to the spinal cord: reticulospinal, interstitiospinal, vestibulospinal and rubrospinal tracts.

The reticulospinal fibres constitute the bulk of the descending fibres. They might be qualified as a final common path by way of which supraspinal influences reach the spinal motoneurons. The prosencephalon probably acts indirectly on the spinal cord via the mesencephalic reticular formation.

Just like the reticulospinal fibres the vestibulospinal tract consists mainly of coarse fibres. This fibre system descends via the ventral funiculus and in part like the reticulospinal and interstitiospinal fibres by way of the f.l.m.

The rubrospinal tract is composed of medium-sized fibres and descends via the lateral funiculus. In the Häggqvist material this tract could only be demonstrated in the lizard Tupinambis nigropunctatus.

No evidence for the presence of a tectospinal tract has been found in the Häggqvist preparations.

This study of normal material has furnished the basis for the experimental investigations to be described in the next chapters.

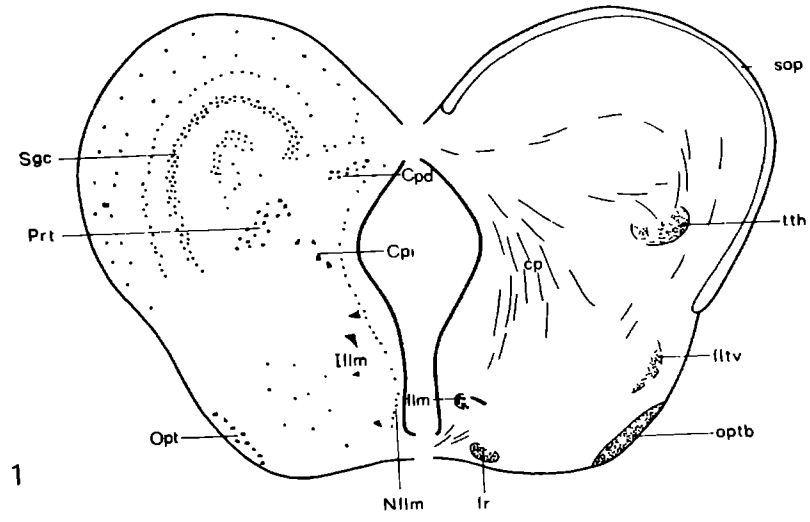
Abbreviations:

Amb	, nucleus ambiguus
Bi	, nucleus of Bischoff
bc	, brachium conjuctivum
Cd	, cornu dorsale (of the spinal cord)
Cerl	, nucleus cerebelli lateralis
Cerm	, nucleus cerebelli medialis
Codm	, nucleus cochlearis dorsalis magnocellularis
Coer	, locus coeruleus
Coi	, nucleus commissurae infimae
Colm	, nucleus cochlearis laminaris
Cpd	, nucleus dorsalis commissurae posterioris
Cpi	, nucleus interstitialis commissurae posterioris
Cv	, cornu ventrale (of the spinal cord)
cereb	, cerebellum
cp	, commissura posterior
dlm	, decussatio lemnisci medialis
EW	, nucleus of Edinger-Westphal
Fl	, nucleus funiculi lateralis
Fun	, nucleus funiculi dorsalis
Funl	, nucleus funiculi dorsalis pars lateralis
Funm	, nucleus funiculi dorsalis pars medialis
fap	, fibrae arcuatae profundae cochleares
fd	, funiculus dorsalis
fl	, funiculus lateralis
flm	, fasciculus longitudinalis medialis
fpd	, fasciculus predorsalis
fr	, fasciculus retroflexus
fltv	, fasciculus lateralis telencephali, pedunculus ventralis
fmt	, fasciculus medialis telencephali
Gc	, griseum centrale
Ico	, nucleus intercollicularis
Iflm	, nucleus interstitialis of the flm
Ipd	, nucleus interpeduncularis, pars dorsalis
Ipv	, nucleus interpeduncularis, pars ventralis
Ism	, nucleus isthmi, pars magnocellularis
Isp	, nucleus isthmi, pars parvocellularis
Ll	, nucleus lemnisci lateralis
Lld	, nucleus lemnisci lateralis, pars dorsalis
Llv	, nucleus lemnisci lateralis, pars ventralis
ll	, lemniscus lateralis
lm	, lemniscus medialis
ls	, lemniscus spinalis
Marg	, nucleus marginalis
mps	, mesencephalic periventricular system
mt	, tractus mamillotegmentalis
Nflm	, nucleus of the flm

n III	, nervus oculomotorius
n IV	, nervus trochlearis
n V	, nervus trigeminus
n VI	, nervus abducens
n VII	, nervus facialis
n VIII	, nervus octavus
n VIIIc	, nervus octavus, radix cochlearis
n VIIIv	, nervus octavus, radix vestibularis
n VIIIva	, nervus octavus, radix vestibularis ascendens
n VIIIvd	, nervus octavus, radix vestibularis descendens
n X	, nervus vagus
n XII	, nervus hypoglossus
Ols	, oliva superior
Opt	, nucleus opticus tegmenti
optb	, tractus opticus basalis
Pm	, nucleus parvocellularis medialis
Prm	, nucleus profundus mesencephali
Prt	, nucleus pretectalis
Rai	, nucleus raphes inferior
Ras	, nucleus raphes superior
Ri	, nucleus reticularis inferior
Ris	, nucleus reticularis isthmi
Rm	, nucleus reticularis medius
Rs	, nucleus reticularis superior
Rub	, nucleus ruber
rd	, radix dorsalis
resp	, fibrae reticulospinales
rusp	, tractus rubrospinalis
rv	, radix ventralis
rVme	, radix mesencephalicus n. trigemini
Sfgs	, stratum fibrosum et griseum superficiale
Sgc	, stratum griseum centrale
Sgp	, stratum griseum periventriculare
Sn	, substantia nigra
Sol	, nucleus tractus solitarii
Strgr	, stratum granulare (cerebelli)
Strm	, stratum moleculare (cerebelli)
Strp	, stratum Purkinje (cerebelli)
sac	, stratum album centrale
sfp	, stratum fibrosum periventriculare
sop	, stratum opticum
spcd	, tractus spinocerebellaris dorsalis
spcv	, tractus spinocerebellaris ventralis
Torc	, torus semicircularis, nucleus centralis
Torl	, torus semicircularis, nucleus laminaris
tbd	, tractus tectobulbaris dorsalis
tbi	, tractus tectobulbaris intermedius
tbv	, tractus tectobulbaris ventralis
tect	, tectum mesencephali
tor	, torus semicircularis

trsol , tractus solitarius
trVds , tractus descendens n. trigemini
tth , tractus tectothalamicus
Vedl , nucleus vestibularis dorsolateralis
Veds , nucleus vestibularis descendens
Ves , nucleus vestibularis superior
Vetg , nucleus vestibularis tangentialis
Vevl , nucleus vestibularis ventrolateralis
Vevm , nucleus vestibularis ventromedialis
Visc , nucleus visceralis secundarius
vecer , fibrae vestibulocerebellares
vespl , tractus vestibulospinalis lateralis
III , nucleus nervi oculomotorii
IIId , nucleus nervi oculomotorii, pars dorsalis
IIIi , nucleus nervi oculomotorii, pars intermedia
IIIv , nucleus nervi oculomotorii, pars ventralis
IV , nucleus nervi trochlearis
Vds , nucleus descendens nervi trigemini
Vm , nucleus motorius nervi trigemini
Vmd , nucleus motorius nervi trigemini, pars dorsalis
Vme , nucleus mesencephalicus nervi trigemini
Vmv , nucleus motorius nervi trigemini, pars ventralis
Vpr , nucleus princeps nervi trigemini
VI , nucleus nervi abducentis
VIIm , nucleus motorius nervi facialis
VIImd , nucleus motorius nervi facialis, pars dorsalis
VIImv , nucleus motorius nervi facialis, pars ventralis
Xmd , nucleus motorius dorsalis nervi vagi
XII , nucleus nervi hypoglossi

Figs. 1-34. ATLAS OF THE BRAIN STEM OF REPTILES.
Diagrammatic representations of transverse sections through consecutive levels of the brain stem and through the first segment of the spinal cord in:
- the turtle Testudo hermanni: figs. 1-10;
- the lizard Tupinambis nigropunctatus: figs. 12-22;
- the snake Python reticulatus: figs. 24-33.
At the left the cell picture, based on a Nissl-stained series; at the right the fibre systems based on Häggqvist preparations. The levels of these figures have been indicated in topographical reconstructions of the brain stem (figs. 11, 23, 34).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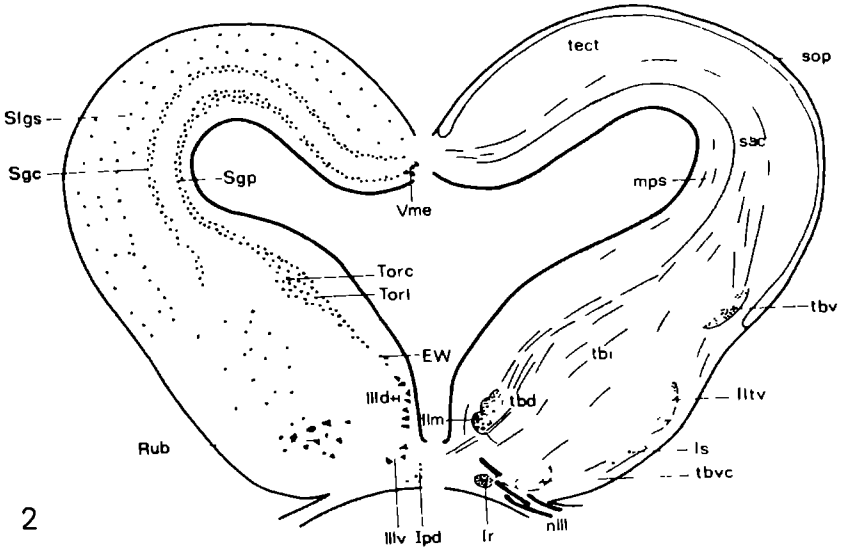
Prt
Cpi
cp
IIIlm
IIltv
IIlm
Opt
optb
NIIIm
Ir

1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Sgp
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mps
Vme
Torc
Torl
tbv
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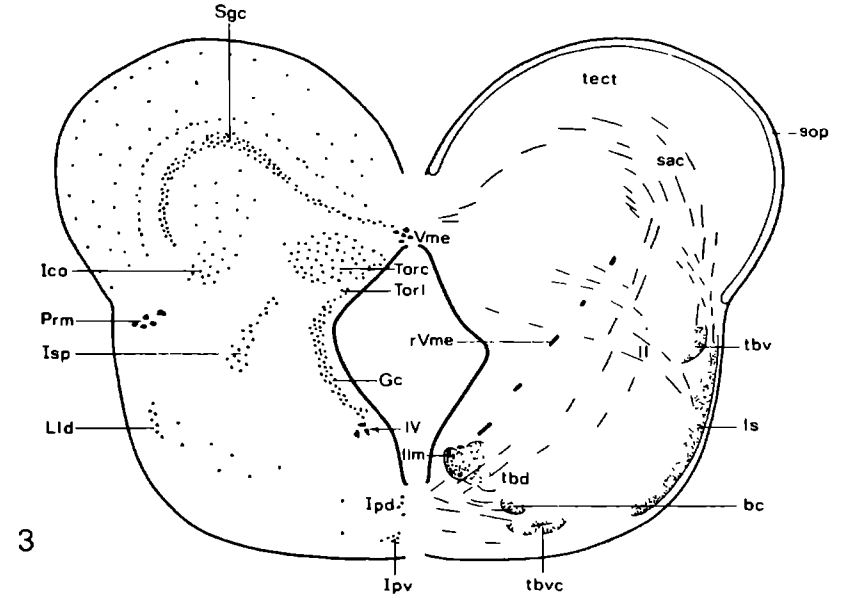
IIltv
IIlm
tbd
Rub
ls
tbvc
IIIv
Ipd
Ir
nIII

2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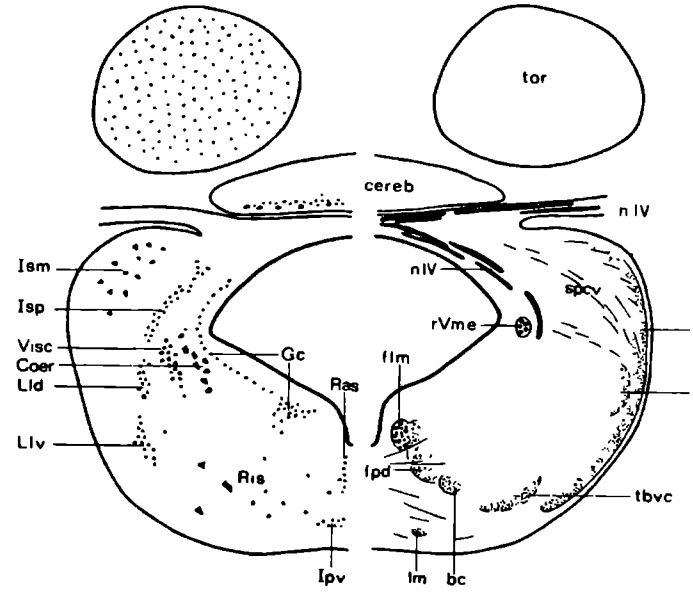
sac
Vme
Ico
Torc
Torl
Prm
rVme
tbv
Isp
Gc
Lld
IV
ls
IIIm
tbd
Ipd
bc
Ipv
tbvc

3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n IV
Ism
Isp
Visc
Coer
Lld
Llv
Gc
Ras
Ris
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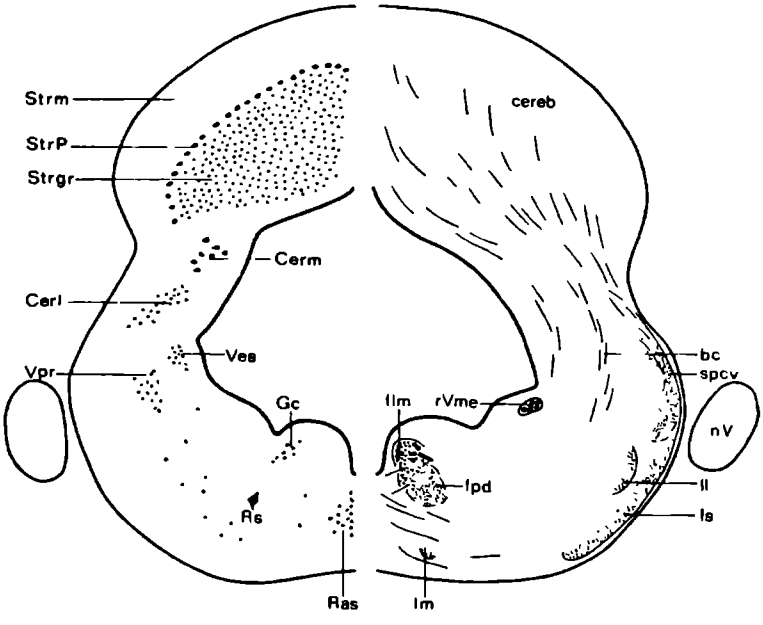
spcv
rVme
ls
flm
ll
fpd
tbvc
lpv
lm
bc

4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Strgr
Cerm
Cerl
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Rs
Ras
cereb
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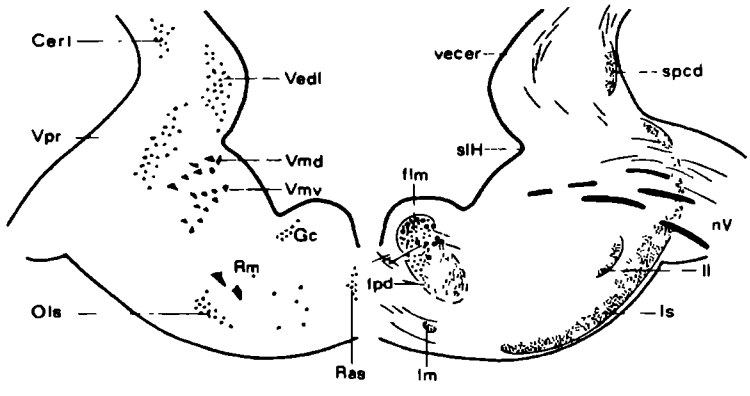
ls
lm

5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fpd
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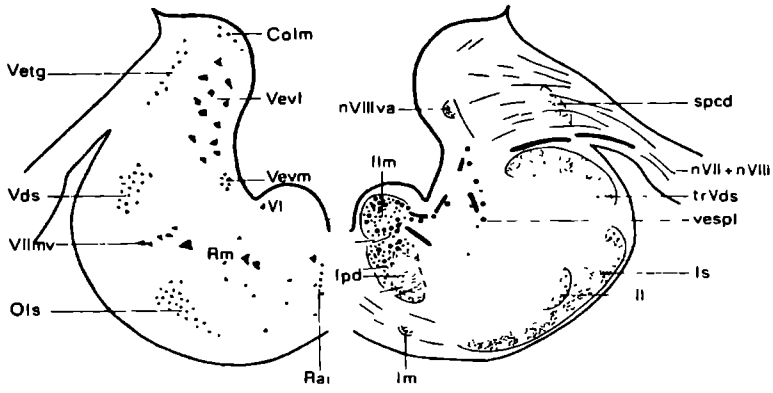
6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Vevl
Vevm
Vds
VI
VIIImv
Rm
Ols
Rai
nVIIIva
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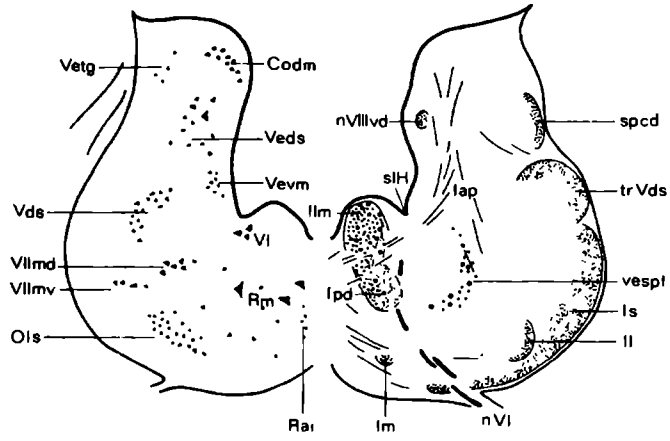
IIm
nVII+nVIII
trVds
vespl
Ipd
Is
II
Im

7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Vevm
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VIImv
Rm
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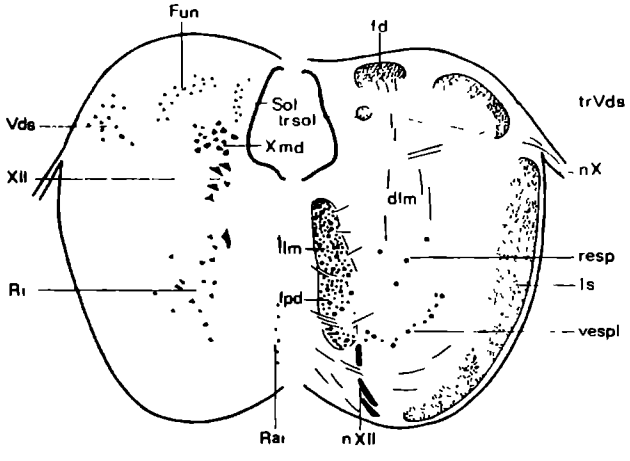
Iap
trVds
IIm
Ipd
vespl
Is
II
Im
nVI

8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Ri
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resp
Is
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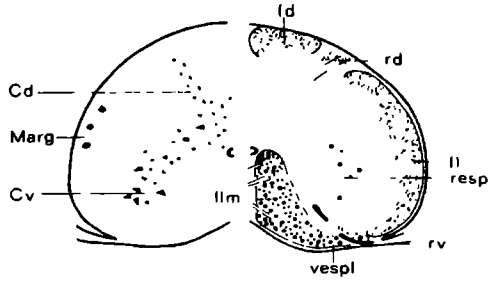
vespl
Rai
nXII

9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Cd
Marg
Cv
IIm
II
resp
rv
vespl

10

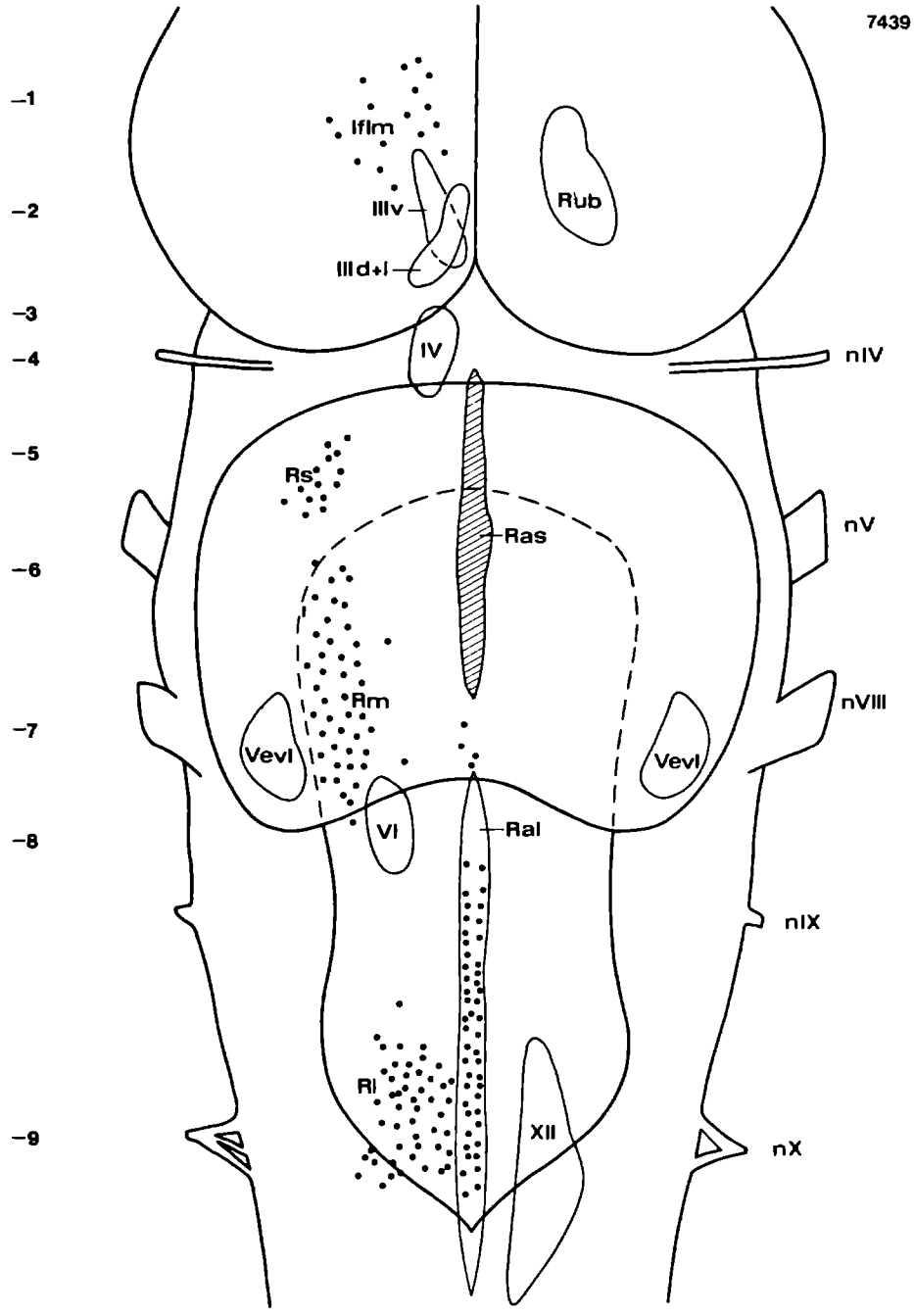
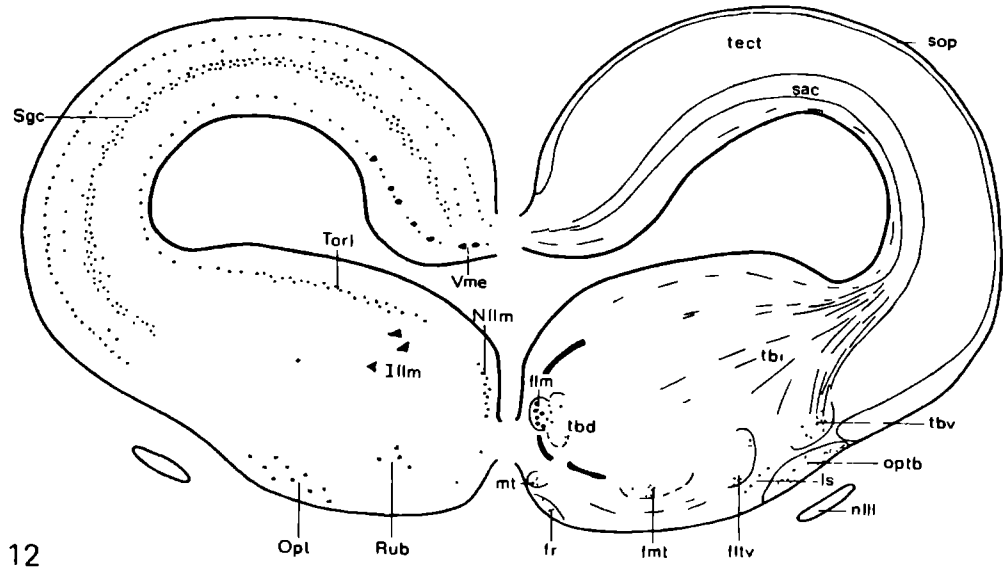


Fig. 11: Topographical reconstruction, showing cell masses of the brain stem and particularly the magnocellular elements of the reticular formation, of the turtle Testudo hermanni, as projected upon a horizontal plane. Numbers on the scale at the side of the drawing correspond to figures of the same number and indicate the levels of the transverse sections in these figures. As filled circles the magnocellular elements of the reticular formation are indicated, to reduce crowding, about one out of five cells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Sgc
Torl
Vme
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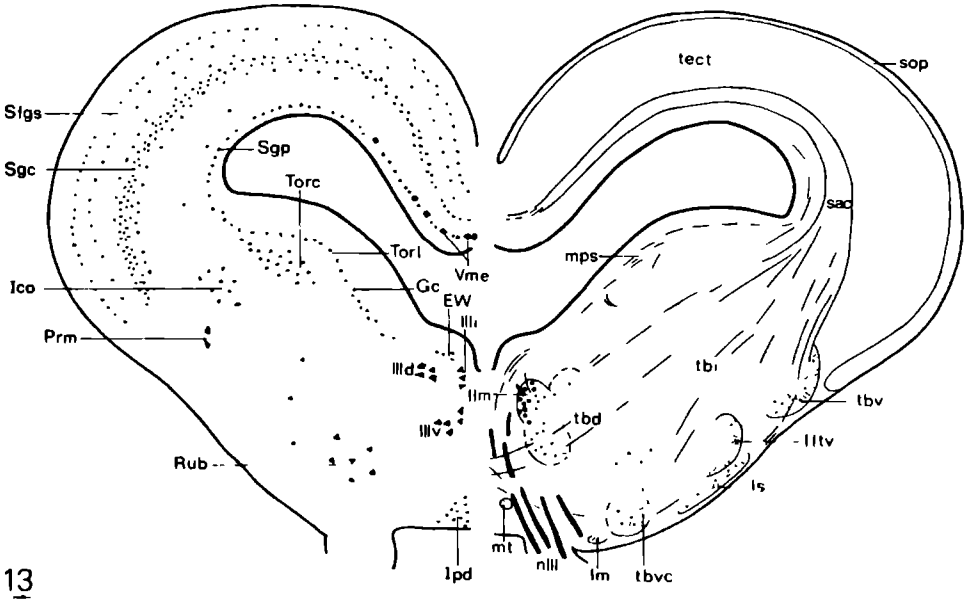
IIIm
tbl
IIm
tbd
tbv
optb
mt
ls
nIII
Opl
Rub
fr
fmt
IIItv

12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Sgp
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Torl
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mps
Ico
Gc
EW
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tbv
tbd
IIItv
IIIv
Rub
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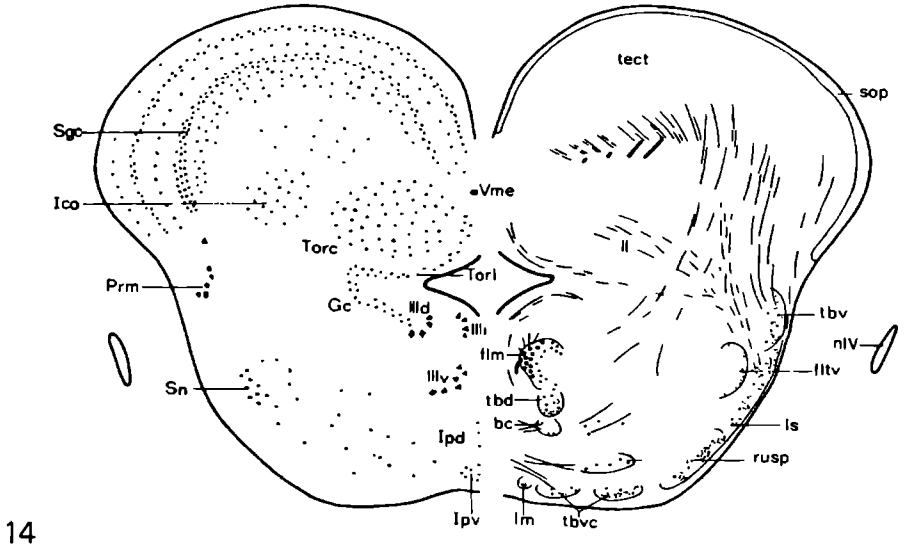
tbvc
Ipd

13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tbv
Gc
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IIm
IIItv
Sn
IIIv
tbd
bc
ls
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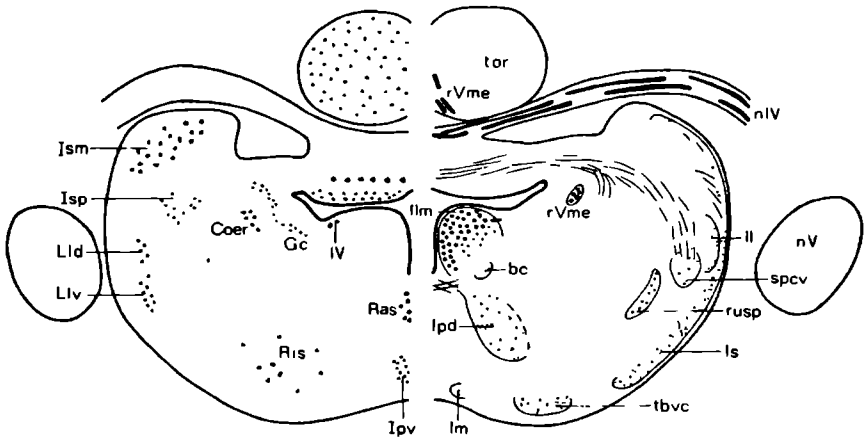
rusp
Ipv
lm
tbvc

14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Ism
Isp
Coer
Gc
IV
llm
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II
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bc
spcv
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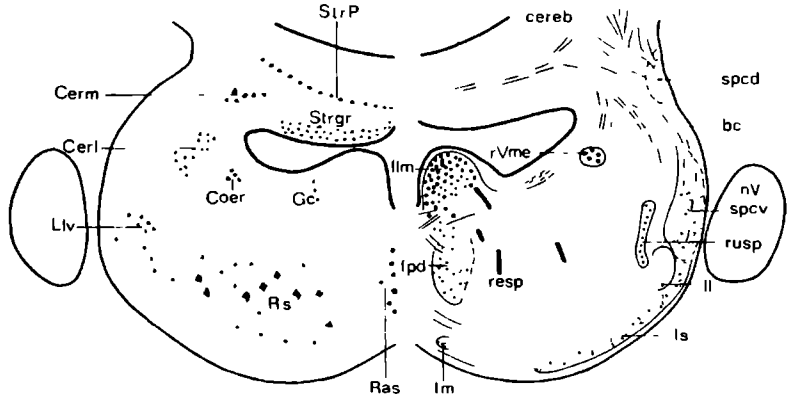
LIv
Ras
lpd
rusp
Ris
ls
tbvc
Ipv
lm

15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lpd
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Rs
ls
Ras
lm

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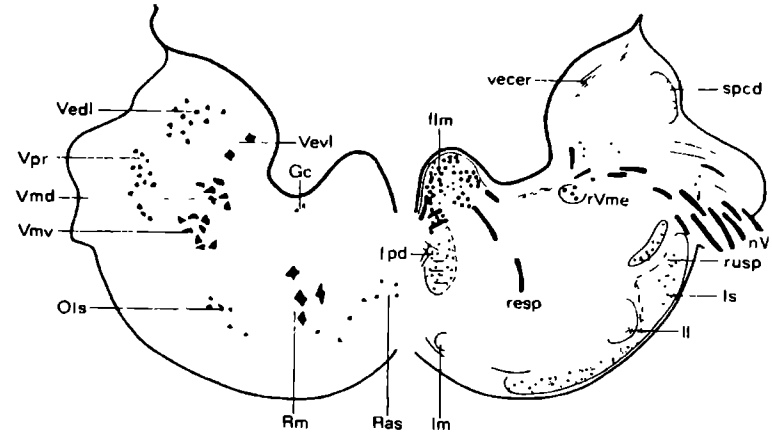
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Ols
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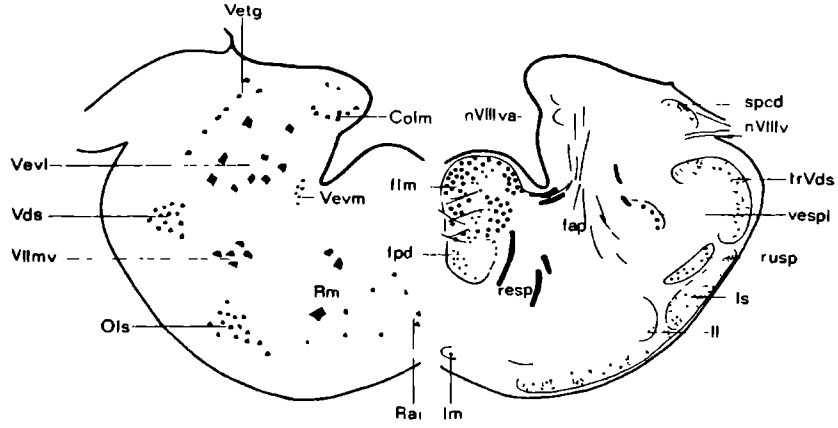
Rm
Ras
lm

17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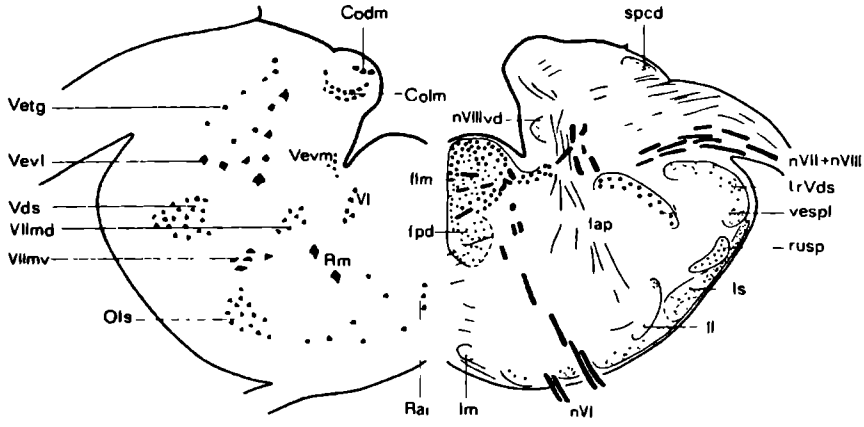
ls
Ols
II
Ral
lm

18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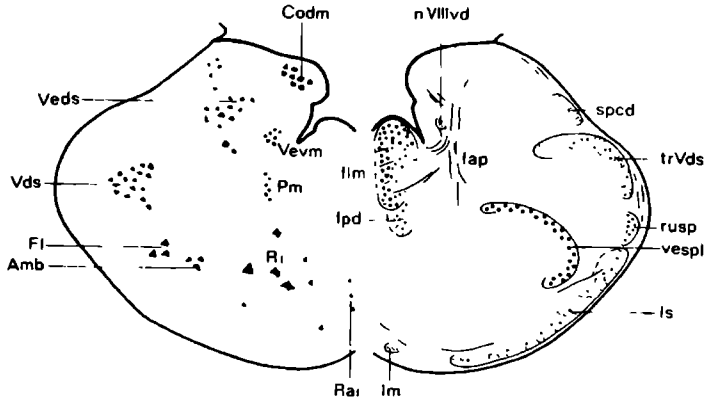
VIImv
Rm
ls
Ols
II
Rai
Im
nVI

19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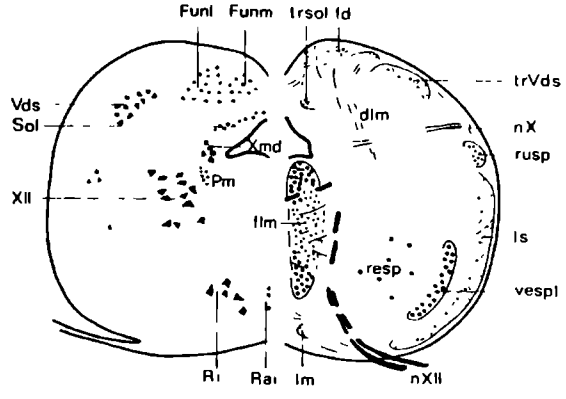
Ri
ls
Rai
Im

20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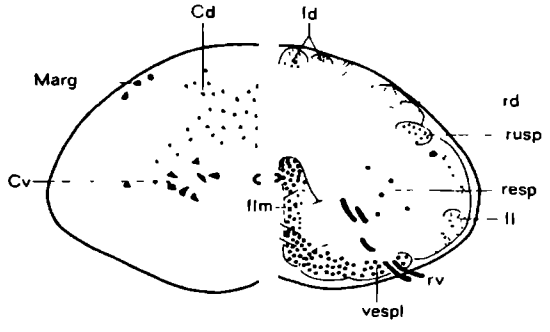
Rai
Im
nXII

21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Cv
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II
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vespl

22

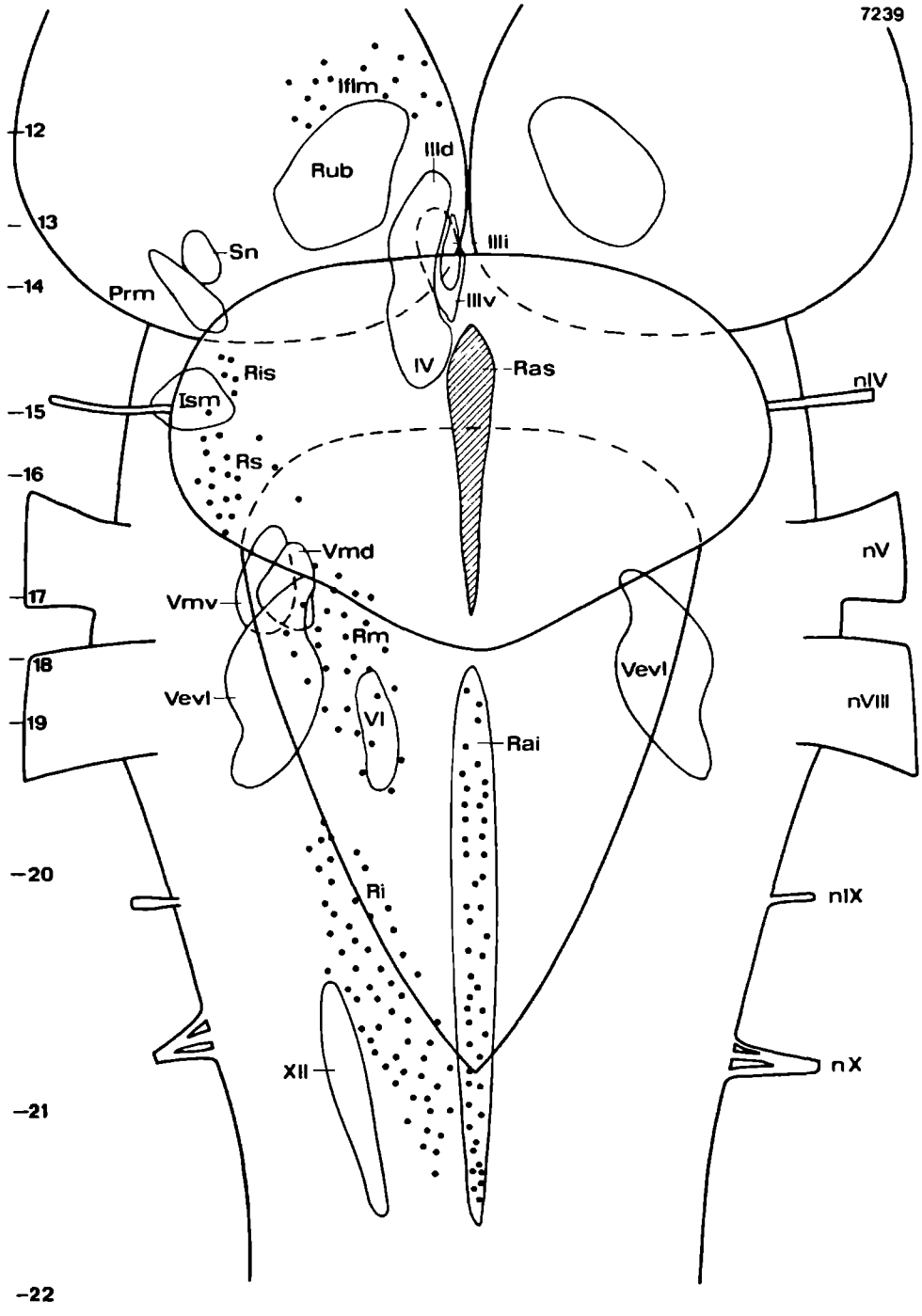
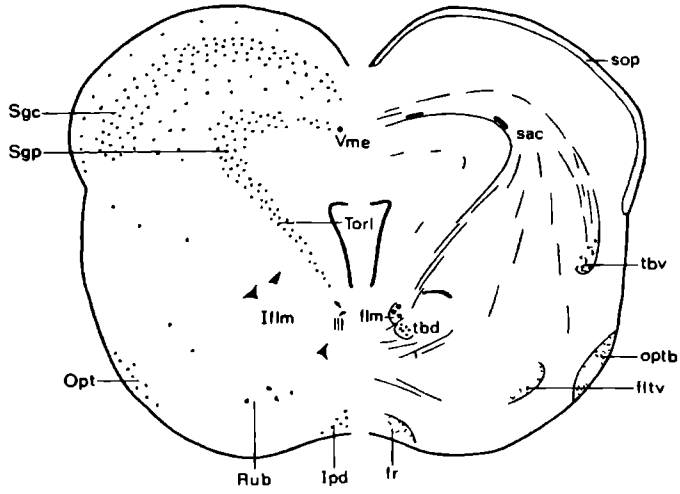


Fig. 23: Topographical reconstruction, showing particularly the magnocellular elements of the reticular formation of the lizard Tupinambis nigropunctatus, as projected upon a horizontal plane. For code cf. fig. 11.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III
flm
tbd
optb
Opt
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Rub
Ipd
fr

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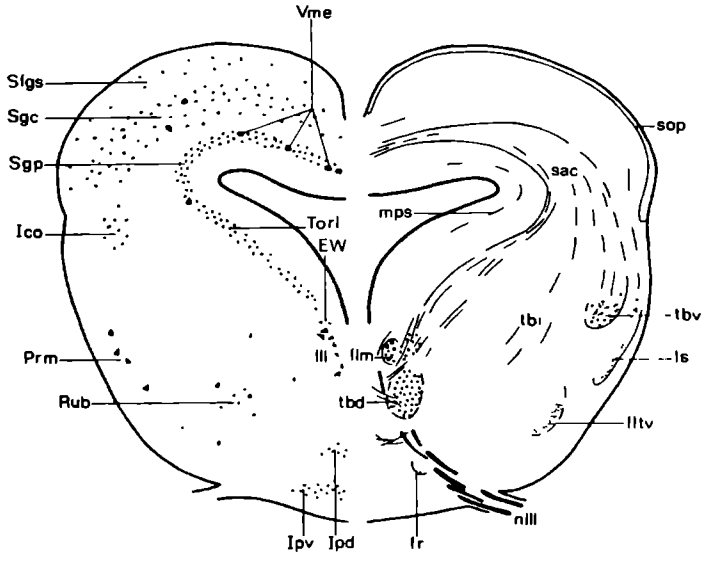
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Sgp
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mps
Torl
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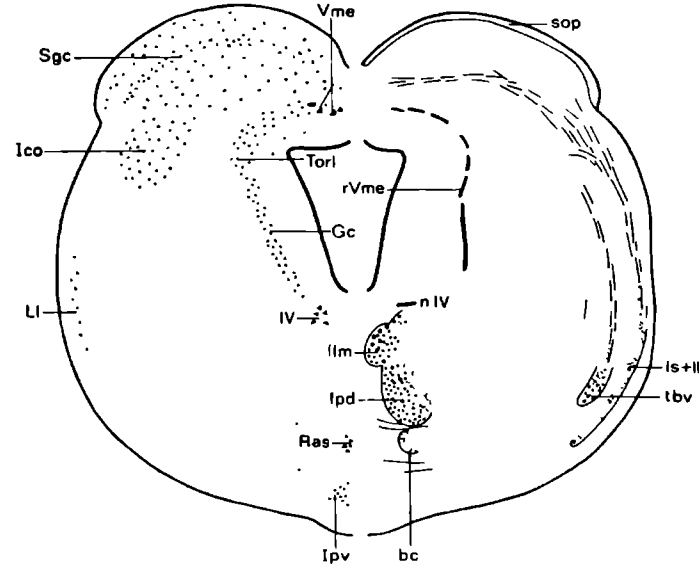
EW
tbv
tbd
ls
Prm
III
flm
Rub
tbd
IIItv
nIII
Ipv
Ipd
fr

25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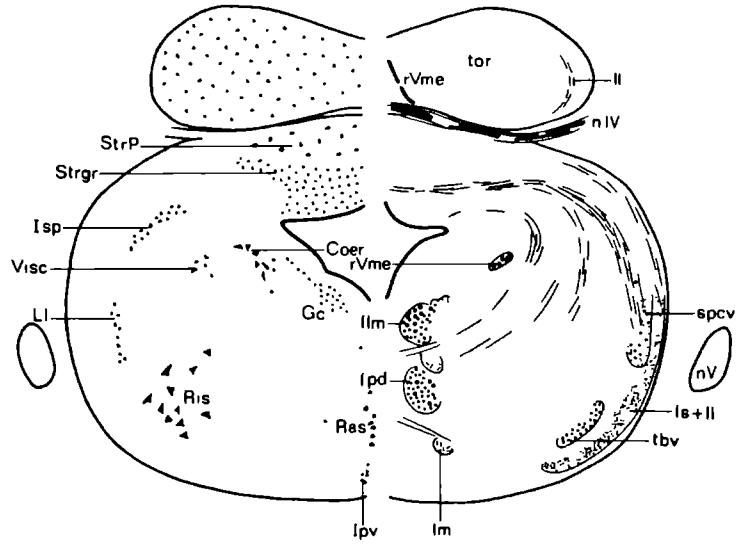
tbv
fpd
Ras
Ipv
bc

26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Strgr
Isp
Visc
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Gc
LI
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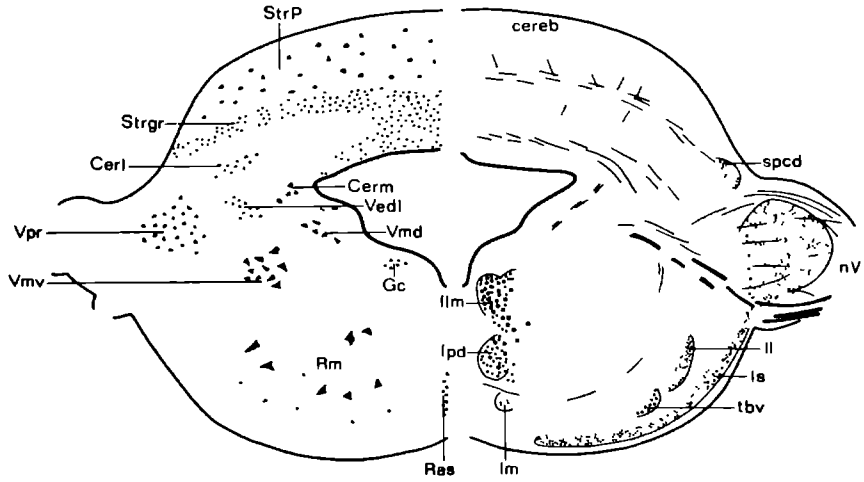
Ipd
Ris
Ras
Is+II
tbv
Ipv
Im

27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Strgr
Cerl
Cerm
Vedl
Vpr
Vmd
Vmv
Gc
spcd
nV
IIm
Ipd
II
Is
Rm
tbv
Ras
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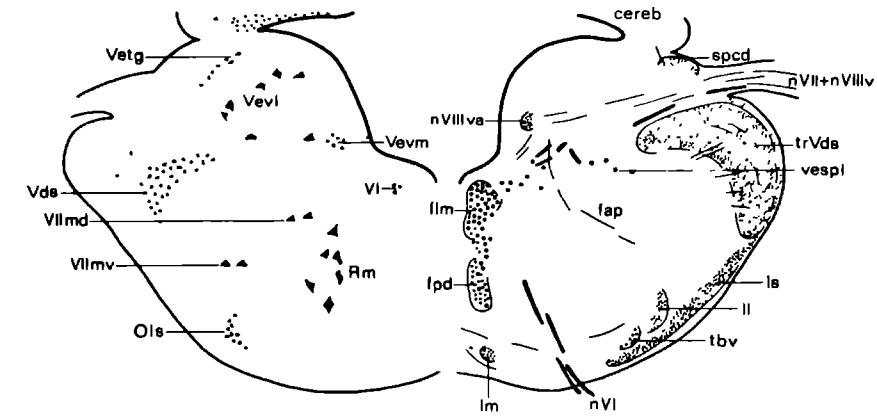
28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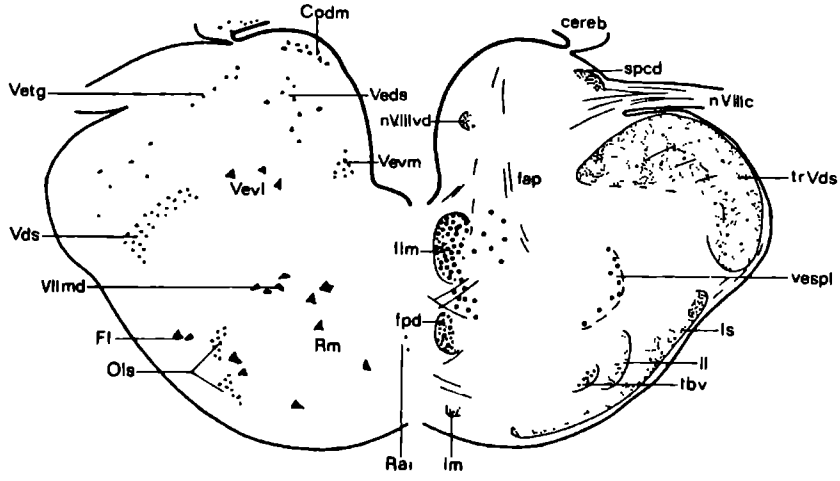
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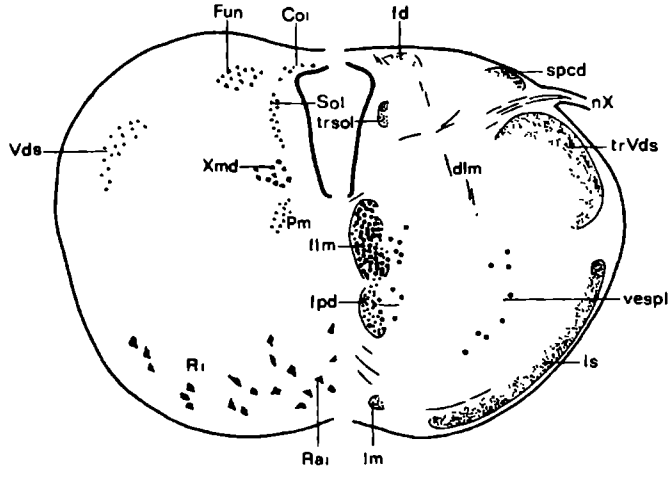
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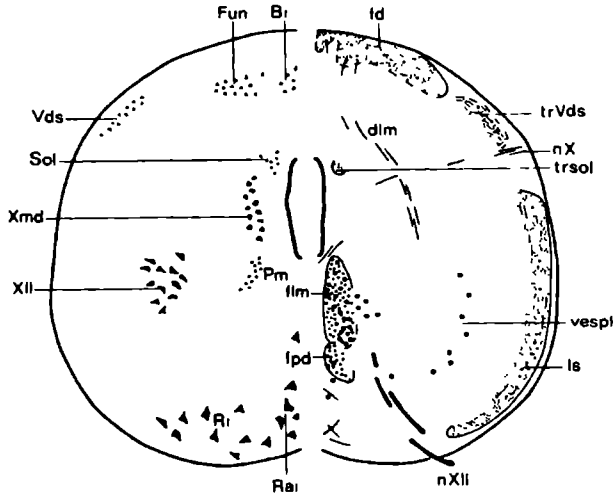
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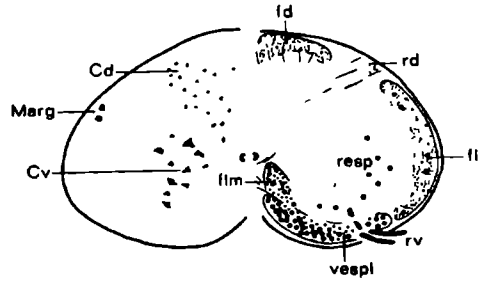
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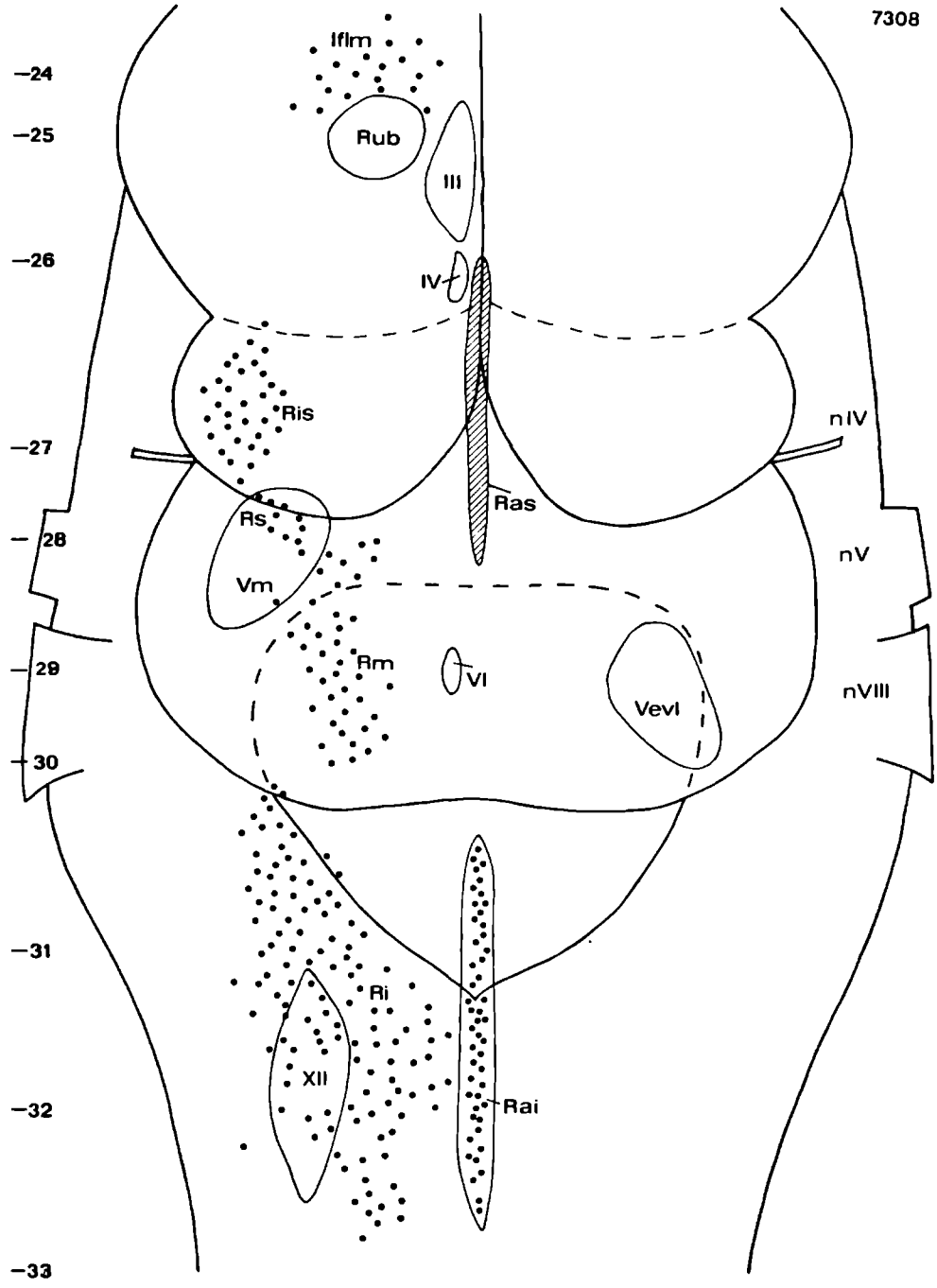


Fig. 34: Topographical reconstruction, showing in particular the magnocellular elements of the reticular formation of the snake Python reticulatus, as projected upon a horizontal plane. For code cf. fig. 11.

IV NOTES ON THE SPINAL CORD

The reptiles studied show profound differences with regard to shape and development of the trunk, tail and extremities. These differences are clearly reflected in the gross structure of the spinal cord (cf. fig. 36). In forms without extremities, as the snake, the cord shows no cervical or lumbar intumescentiae, but these enlargements are well marked in the lizard. Distinct intumescences also occur in turtles - in these forms the thoracic region of the cord is, however, strikingly thin as a consequence of the absence of trunk musculature as well as of the relatively small sensory supply of the shell (de Lange, '17).

In reptiles the cord extends throughout the whole vertebral canal. In the turtle it consists of some 40 segments: 8 cervical, 15 thoracolumbar, 2 sacral and 16 caudal (tail) segments. In the lizard Tupinambis also 8 cervical segments can be distinguished, and in addition 17 thoracolumbar (12 thoracal and 5 lumbar), 2 sacral and about 50 caudal elements. All modern reptiles with well developed limbs possess two sacral vertebrae (Bellairs, '70). The spinal cord of the snake Python consists of some 200-220 precaudal (dorsal) segments and about 30 caudal (tail) ones.

The gray matter of the spinal cord shows a clear division into ventral and dorsal horns. Before discussing the various cell groups of the spinal cord a few notes on the primary afferents to the gray matter, i.e., the dorsal root, will be made.

It is known that in reptiles, as in mammals, each dorsal root (radix dorsalis) can be divided into a coarse-fibred medial and a thin-fibred lateral bundle (Ariëns Kappers et al., '36). A certain proportion of the primary afferent fibres of the former bundle enters the funiculus dorsalis and travels rostrally to reach the dorsal funicular nuclei.

Most of these primary afferent fibres terminate, however, in the dorsal and intermediate gray, as has been experimentally shown by Goldby and Robinson ('62) in Lacerta viridis and by Joseph and Whitlock ('68a) in Caiman sclerops and in the lizards Ctenosaura hemi-

lopha and Iguana iguana. In addition in the latter lizards these fibres could be traced along the lateral margin of the ventral horn and in several instances appeared to cascade down along the long dorsal dendrites to a point very close to the somata of the motoneurons (Joseph and Whitlock, '68a).

The gray matter of the spinal cord

In the gray matter of the spinal cord of reptiles various types of cells are found, e.g., funicular cells, commissural neurons and motoneurons (Nieuwenhuys, '64).

Among the funicular and commissural neurons there are large elements which send numerous dendrites into the white matter, but the dendritic trees of others are much more restricted and confined to the gray substance (Banchi, '03). Many of the secondary neurons in the reptilian spinal cord send one of their dendrites across the midline via a posterior commissure dorsal to the central canal. This commissure contains in addition a number of spindle-shaped neurons, the so-called dorsal median cells (Cajal, 1891; Banchi, '03).

The reptilian cord contains, besides these elements with long axons, true internuncial cells of Golgi's type 2 in the dorsal horn (Banchi, '03). They are provided with a rather restricted, but richly ramifying dendritic tree and their axon branches ventral to the cell body in the basal part of the dorsal horn.

The ventral horn cells of the reptilian spinal cord are large and show in the intumescentiae a distinct division into a medial and a lateral column. The dendrites of the motoneurons extend from the gray matter into the ventral and lateral funiculi. In the lateral funiculus these dendrites end in a marginal dendritic plexus. Because of this enormous extent and overlap of the dendritic trees of the motoneurons in the spinal cord, the exact site of termination of the supraspinal fibre systems will be hard to determine.

So far a subdivision of the reptilian spinal gray matter into layers comparable to those in the cat (Rexed, '52, '54) or in the pigeon (van den Akker, '70) has not been possible. In the present

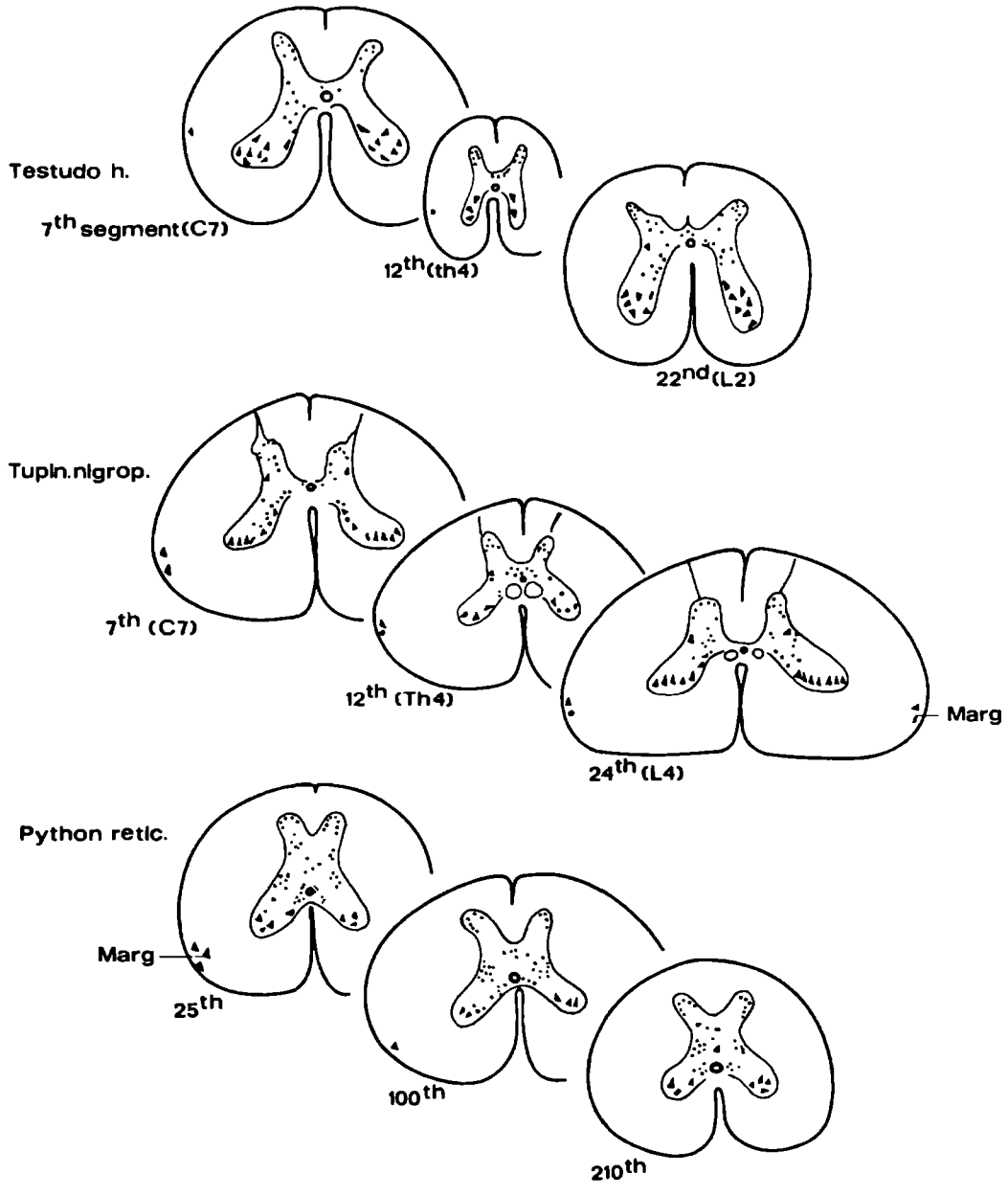


Fig. 35: Diagrammatic representation of transverse sections through representative levels of the spinal cord of Testudo hermanni, Tupinambis nigropunctatus and Python reticulatus, showing the cell picture based on Nissl-stained series.

study the following provisional subdivision will be employed (cf. fig. 35). For convenience of description the different parts of the gray will be called areas, a neutral nomenclature, which can be changed to a more specific one, when more experimental data are available:

1) area a: the dorsal horn, corresponding to the areas 1-3 of van den Akker and to the layers I-V of Rexed;

2) area b: an intermediate zone, corresponding largely to van den Akker's area 4 and probably to the layers VI and VII of Rexed;

3) area c: a central zone, also called substantia grisea centralis, resembling area 6 of van den Akker and layer X of Rexed;

4) area d: the motoneuron area, subdivided into a) a medial zone (area dm), consisting of small and large cells, the latter constituting the medial column of motoneurons related to the innervation of the trunk musculature, and b) a lateral zone (area dl), present only in the cervical and lumbar enlargements; this zone contains the lateral column of motoneurons innervating the extremity muscles. These motoneurons are beautifully lined up in the lizard (cf. fig. 35), whereas they are more or less at random arranged in the turtle. Area d corresponds to the medial part of area 4 and to the area 7 of van den Akker and to the layers VIII and IX of Rexed.

A more detailed study on the cell masses and the fibre pattern of the reptilian spinal cord is now in process in the present laboratory.

A peculiarity of the reptilian cord is the presence of nerve cells in the marginal dendritic net, dorsal to the ventral root (cf. figs. 10, 22, 33, 35). These 'outlying' neurons constitute a column extending throughout the cord, although almost interrupted at the emergence of each spinal root (Nieuwenhuys, '64). Axons of these nuclei marginales, also called nuclei of Gaskell or nuclei of Hoffmann-Kölliker, have been traced by Terni ('26) into the ipsilateral lateral funiculus and into the anterior commissure. It is not known, however, where these fibres terminate.

Fibre systems in the spinal cord

A few remarks concerning the fibres which constitute the white matter of the reptilian cord will now be made.

The dorsal funiculi consist largely of ascending and descending propriospinal fibres (Ariëns Kappers et al., '36), but they also contain long ascending axons which reach the medulla oblongata. These long ascending fibres are somatotopically arranged in such a fashion that fibres of caudal origin are most medial and those joining at more rostral levels are situated more laterally (Goldby and Robinson, '62; Ebbesson, '67, '69; Joseph and Whitlock, '68b). After transection of the dorsal funiculus most of the long ascending dorsal funicular fibres appear to terminate in the nucleus funiculi dorsalis (Ebbesson, '67, '69).

The lateral funiculi contain, in addition to fasciculi proprii, several long ascending systems. Investigators working with normal material have described spinocerebellar, spinobulbar and spinotectal fibres. The latter two components have been designated by Ebbesson ('67) as the lemniscus spinalis, a term which has been introduced by Herrick ('14, '30 and '48) in his extensive descriptions of the urodelan brain.

The experimental work of Ebbesson ('67, '69) in the lizard, turtle and snake has shown that the bulk of the fibres of the spinal lemniscus terminate in the ipsilateral reticular formation, more particularly in the nucleus reticularis inferior and the caudal part of the nucleus reticularis medius. A much less dense projection was demonstrated to the rostral part of the latter nucleus and to the nucleus reticularis superior. Besides these spinoreticular fibres, Ebbesson ('67, '69) demonstrated various other projections of the lateral funiculus, viz. to some nuclei of the brain stem (the nucleus parvocellularis medialis, the nucleus motorius n. facialis, the nucleus motorius dorsalis n. vagi and the vestibular nuclei), to the mesencephalon and even a very small spinothalamic component.

It has already been mentioned that the lateral funiculus also contains descending fibres from the reticular formation and a rubro-

spinal tract, the latter at least in the lizard.

The ventral funiculus contains the bulk of the descending fibres from the brain stem: reticulospinal as well as vestibulospinal.

It is noteworthy that in many reptiles the ventral funiculi are traversed by an accessory commissure, which carries dendrites of motoneurons and axons of commissural cells (Nieuwenhuys, '64).

The portion of the ventral funiculus lying dorsal to this accessory commissure consists of particularly coarse fibres and is a direct continuation of the fasciculus longitudinalis medialis in the brain stem. The supraspinal components of this complex bundle have been described by Terni ('21), who observed: 1) ascending fibres, originating from large, multipolar dorsal horn cells, 2) ascending, descending and bifurcating fibres from similar elements situated in the ventral horn, and 3) axons of motor and funicular cells, which run for a short distance in the bundle in question.

V THE ORIGIN OF THE FIBRE SYSTEMS DESCENDING TO THE SPINAL CORD

a) Analysis of retrograde cell changes following spinal cord lesions:

In order to locate the sites of origin of the pathways descending from the brain stem to the spinal cord, hemicordotomies have been made at various levels (indicated in fig. 36) and the ensuing retrograde cell changes have been studied in the brain stem. It has already been mentioned that this retrograde technique is the most reliable anatomical procedure for determining the origin of reticulospinal fibres. The cells in the reticular formation are diffusely arranged, hence it may be expected that electrolytic lesions within its confines would destroy fibres of many different sources.

The typical retrograde cell changes include:
1) an obvious dissolution of the large Nissl bodies (chromatolysis). In certain cells a residual Nissl substance remains, largely confined to a narrow peripheral zone (Lieberman, '71); 2) swelling of the perikaryon; and 3) a peripheral displacement (eccentricity) of the nucleus. The latter sign showed to be of only minor importance.

The above changes were described as 'primäre Reizung' by Nissl (1892, 1894), as 'réaction à distance' (Marinesco, 1898) or as acute or early retrograde degeneration (Brodal, '39, '40, '57). Commonly, however, solely the term chromatolysis is used.

Early changes after severance of the axon can vary considerably in intensity. Usually they are clearer in very young animals than in adults (Brodal, '39, '40, '57). In mammals the acute retrograde cell changes are most pronounced between 1 and 3 weeks after axotomy. In reptiles, however, a considerably larger survival time is necessary, in the lizard Lacerta viridis at least 3 weeks (Robinson, '69).

Retrograde cell changes were observed only in the large elements. However, the absence of chromatolysis in small cells should be interpreted with reservation because of the extreme difficulty in judging retrograde changes in such neurons (Beran and Martin, '71). Areas have therefore been interpreted as containing neurons projecting to the spinal cord only, when they harbor cells showing typical acute retro-

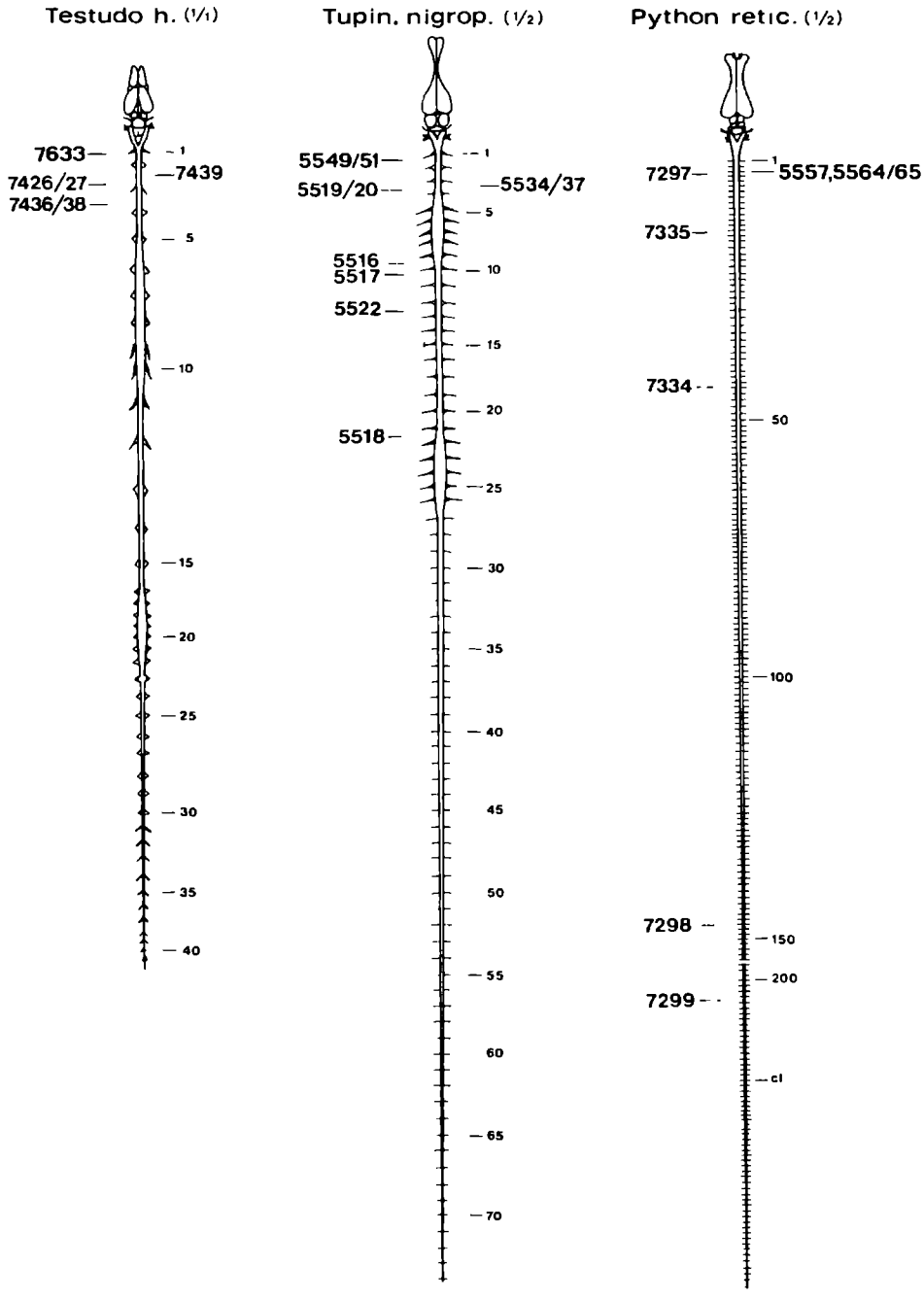


Fig. 36: Schematic representation of the central nervous system in Testudo hermanni, Tupinambis nigropunctatus and Python reticulatus, showing in particular the number and distribution of spinal segments. In addition the sites of the hemicordotomies carried out are indicated. Abbrev.: cl = level of cloaca.

grade changes.

In no case an unequivocal reduction in the number of cells within groups showing retrograde cell changes could be demonstrated, not even in some long-term experiments in the lizard Tupinambis (survival times of 60 and 90 days).

It should also be stated beforehand that cell changes were never observed in the brain stem reticular formation or in any other centre in the brain stem projecting to the spinal cord, following hemisections more caudally than high thoracic segments in the lizard or lesions in the 42nd segment or even more caudally in the snake. The most plausible explanation for this apparent resistance to severance of the axon is collateral branching of the latter proximal to the site of the injury, and that these collaterals are in some way capable of protecting the cell against the harmful effect of losing a substantial portion of its cytoplasm (Cajal, '28; Cole, '68; Cragg, '70; Lieberman, '71). Similar negative observations have been made by Beran and Martin ('71) studying the reticulospinal tracts in young opossums.

Recently, neurophysiological evidence has been presented, that in the cat the axons of the vestibulospinal tract do show a considerable collateral branching during their course in the spinal cord (Abzug et al., '73, '74).

The experiments were started with a pilot study in the snake Python reticulatus in order to test the applicability of the retrograde technique in adult reptiles. The Python possesses a very well developed reticular formation, consisting of giant cells, and it is known that such very large neurons react particularly promptly with retrograde changes to the transection of their axons as demonstrated in the cat (Pompeiano and Brodal, '57a; Torvik and Brodal, '57).

Besides in Python hemicordotomies have been made in the turtles Testudo hermanni and Pseudemys scripta elegans, and in the lizard Tupinambis. In the tables 1-3 the extent of the lesions and the ensuing retrograde cell changes are presented in a semiquantitative way. From a representative case of each reptile studied, about one out of five cells showing retrograde cell changes has been indicated

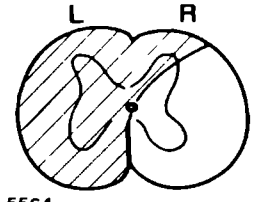
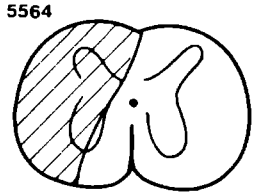
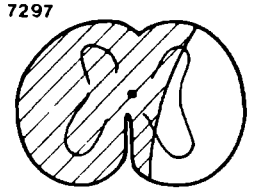
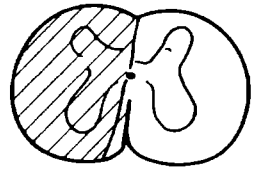
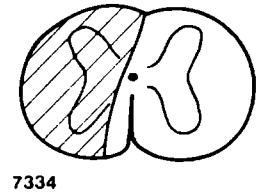
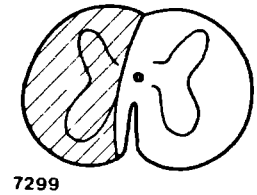
lesion	segment	ST	Rai	Ri		Rm		Rs		Rls		Vevl		Rub	lflm		tm
				L	R	L	R	L	R	L	R	L	R		L	R	
 5564	2	28	++	++	+	++	±	++	±	+++	+	+++	+	-	+	+	-
 7297	3	25	++	+++	++	++	±	+	±	+	±	+	±	-	-	-	-
 5557	3	28	++	+++	++	+++	+	++	+	++	+	+++	++	-	+	+	-
 7335	15	26	++	+++	++	+++	-	++	±	++	+	+++	+	-	-	-	-
 7334	42	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
 7299	205	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Estimates of the retrograde cell changes in brain stem nuclei following spinal cord lesions in Python reticulatus. The extent of the lesions is shown as hatchings. The numbers of cell bodies showing clear-cut retrograde cell changes in a nucleus are indicated approximately as follows: many in each section (> 3)+++, moderate numbers in each section (2-3) ++, one in each section +, a few cells (2-5) in the whole nucleus ±, negative findings -. Abbrev.: ST - survival time (in days); tm - tectum mesencephali; for other abbrev. cf. pg. 17-19.

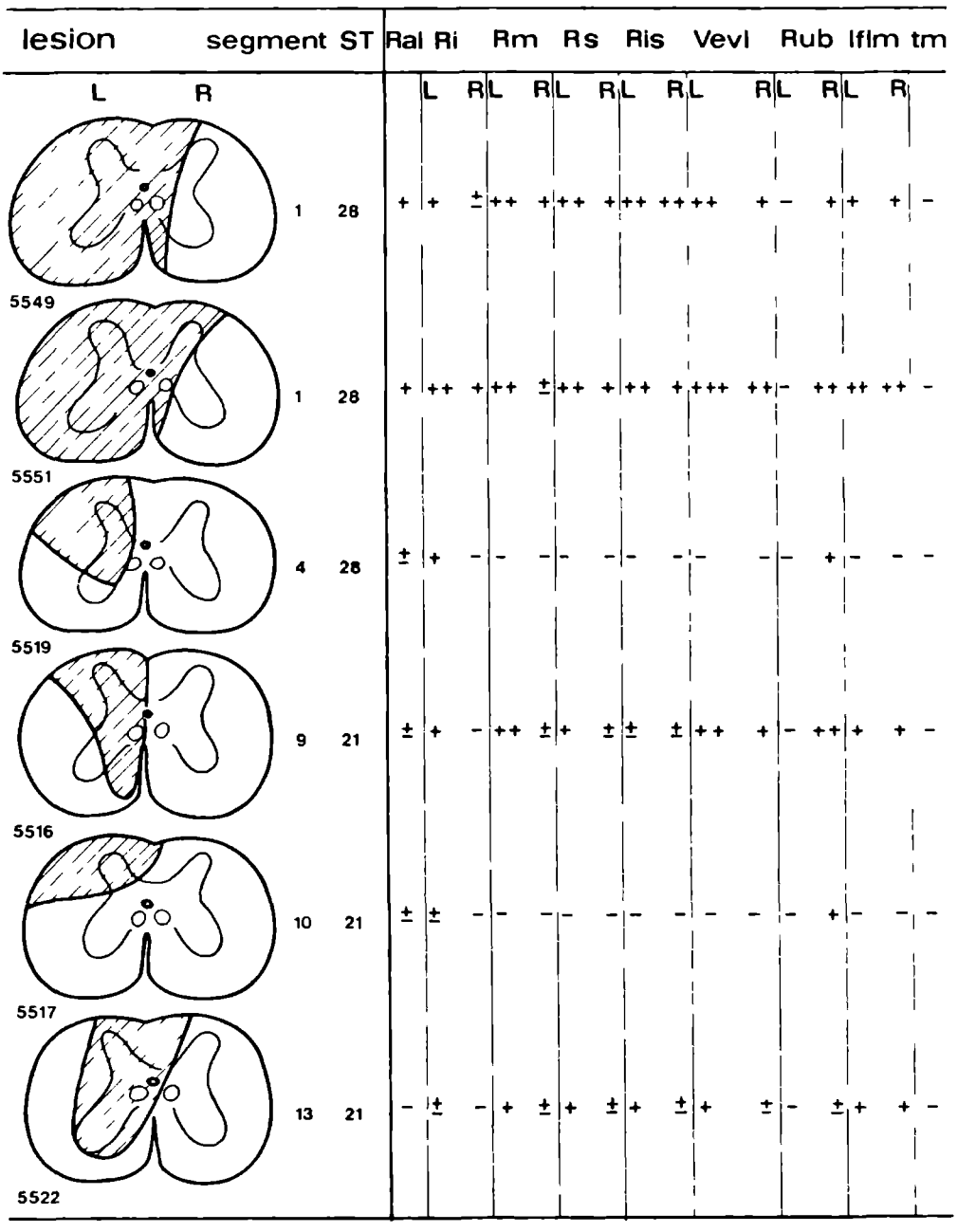
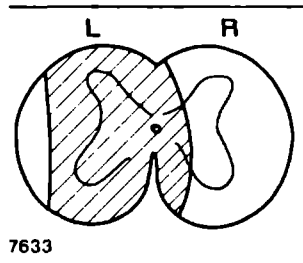
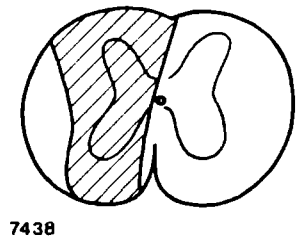
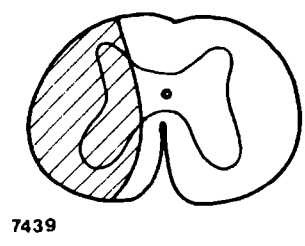


Table 2: Estimates of the retrograde cell changes in brain stem nuclei following spinal cord lesions in Tupinambis nigropunctatus. For code cf. table 1.







lesion	segment	ST	Rai		Ri		Rm		Rs		Ris		Vevl		Rub		Iflm		tm
			L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
7633	1	28	++	++	+	+	+	±	+	+	++	++	-	+	+	+	-
7438	3	21	±	±	-	+	-	±	-	-	-	-	+	±	-	±	+	-	-
7439	4	28	+	+	±	++	-	+	±	-	-	+	±	-	+	-	-	-

Table 3: Estimates of the retrograde cell changes in brain stem nuclei following spinal cord lesions in Pseudemys scripta elegans (cases 7438 and 7439) and in Testudo hermanni (case 7633). For code cf. table 1.

in a diagram as projected upon a horizontal plane (figs. 37-39) in the same way as already done for the reticular formation in the figures 11, 23 and 34. Chromatolytic cells in the reticular formation are shown as filled circles, whereas for the ventrolateral vestibular nucleus and for the red nucleus open circles are used.

Python reticulatus (case 7335): this case concerns an almost complete hemisection of the spinal cord at the 15th spinal segment, only a small part of the ventral funiculus has been spared.

Retrograde cell changes as defined above have been found in the following nuclei (cf. fig. 37 and table 1):

- in the reticular formation: bilateral in the nucleus reticularis

inferior and in the nucleus reticularis isthmi, in the midline in the nucleus raphes inferior and only ipsilateral to the lesion side in the nuclei reticulares medius and superior; approximately 30% of the large cells in the above areas respond retrogradely; no retrograde cell changes were noted in the nucleus raphes superior;
- in the vestibular nuclear complex chromatolysis was restricted to one nucleus, viz., the nucleus vestibularis ventrolateralis, which was bilaterally involved;
- no chromatolytic neurons have been found in the medial part of the tegmentum mesencephali, i.e. the area in which in other reptiles the red nucleus is found, in the interstitial nucleus of the f.l.m., or in the tectum mesencephali. It should, however, be remembered that a small part of the ventral funiculus was not destroyed by the lesion.

From a comparison of the different cases in Python reticulatus (cf. table 1), the following conclusions can be drawn:
1) As regards the reticular formation: comparing case 7297 with case 7335, the fact that more cells showing retrograde changes were noted in case 7335 in the nuclei reticulares medius, - superior and - isthmi, is probably due to the larger involvement of the ventral funiculus in the spinal cord lesion; the nucleus reticularis inferior and the nucleus raphes inferior, however, are not more involved. From these observations it may be inferred that two main areas of origin for reticulospinal fibres can be recognized in the reticular formation: the nucleus reticularis inferior, which projects bilateral to the spinal cord probably mainly by way of the lateral funiculus, whereas the rostral part of the rhombencephalic reticular formation, consisting of the nuclei reticulares medius, - superior, and - isthmi, projects predominantly ipsilateral via the ventral funiculus to the cord.
2) In all cases only one nucleus in the vestibular nuclear complex, viz., the nucleus vestibularis ventrolateralis, showed retrograde cell changes; comparison of case 7297 with cases 7335 and 5564 renders it likely that this nucleus projects bilaterally to the spinal cord by way of the ventral funiculus: in the latter two cases a larger part of the ventral funiculus has been destroyed, resulting in a fairly larger

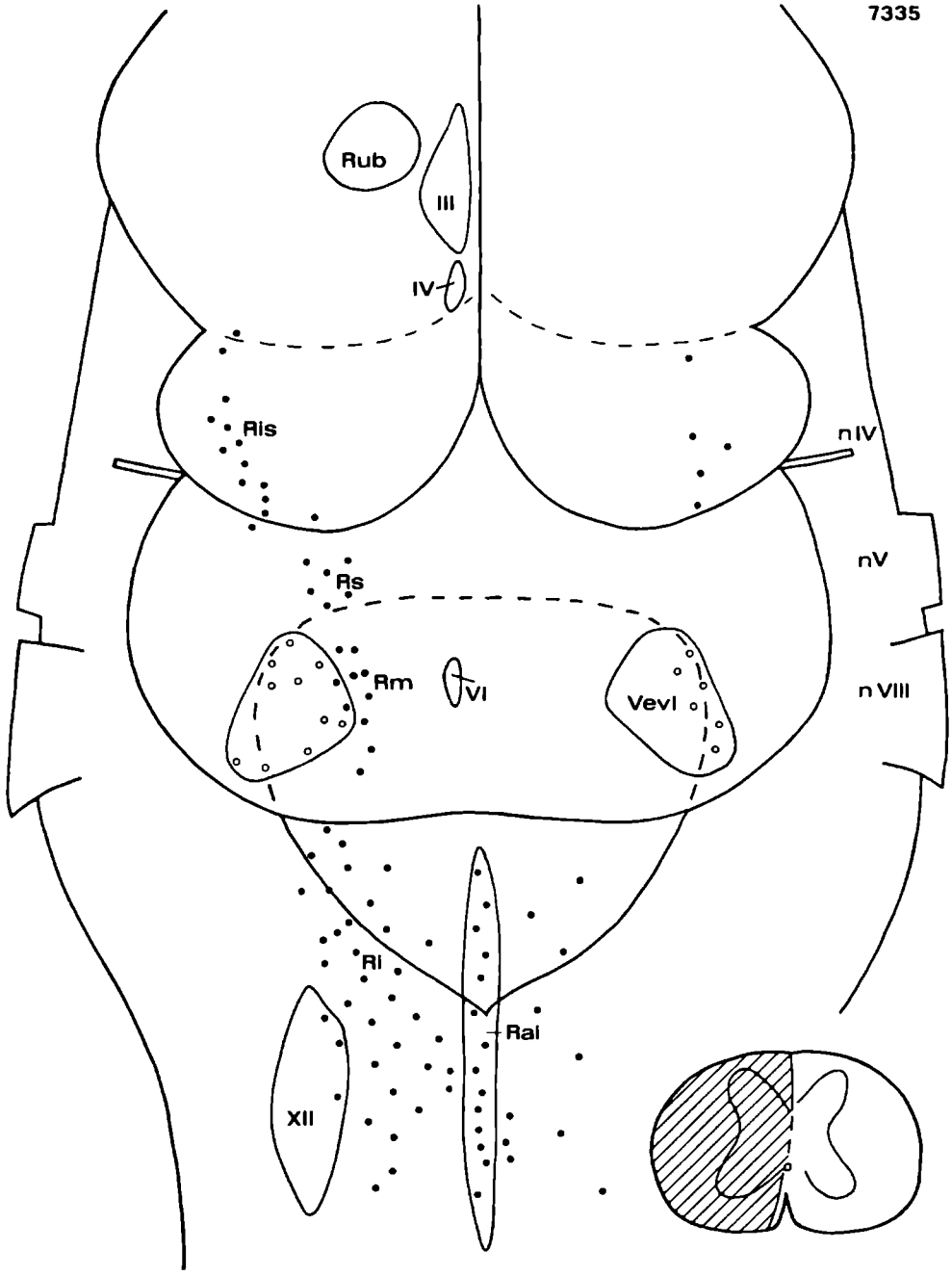


Fig. 37: Topographical reconstruction of the brain stem of Python reticulatus, showing the distribution of the magnocellular cells in which clear-cut retrograde cell changes have been observed following a hemicordotomy. As filled circles the elements in the reticular formation demonstrating chromatolysis are indicated, about one out of five cells; as open circles the same holds for the ventrolateral vestibular nucleus.

number of cells showing chromatolysis.
3) Retrograde cell changes in the interstitial nucleus of the f.l.m. were only noted when the most medial part of the ventral funiculus was involved in the lesion (cases 5557 and 5564).
4) No chromatolytic neurons have been found in the medial part of the tegmentum mesencephali or in the tectum mesencephali in any of these experiments.
5) No chromatolytic changes have been observed following hemisections at the 42nd spinal segment (case 7334) or more caudally (cases 7298 and 7299).

Tupinambis (case 5516): in this series a large part of the lateral funiculus has been spared. Particularly the relative lack of retrograde cell changes in the nucleus reticularis inferior and in the nucleus raphes inferior should be noted (cf. fig. 38), which is probably due to the sparing mentioned above. Chromatolytic cells in the reticular formation are mainly found in the nuclei reticulares medius, - superior and - isthmi, predominantly ipsilateral to the lesion side. As in Python the retrograde cell changes in the vestibular nuclear complex are limited to the nucleus vestibularis ventrolateralis which is bilaterally involved. Other nuclei in which retrograde cell degeneration has been noted are the nucleus interstitialis of the f.l.m. on both sides, and the red nucleus contralateral to the lesion.

From the combination of the results obtained from lesions of various extent in Tupinambis, presented in table 2 it can be concluded that:
1) retrograde cell changes are found in the nucleus reticularis inferior, when the hemisection involves the lateral funiculus; probably the same holds true for the nucleus raphes inferior;
2) as regards the the rostral part of the rhombencephalic reticular formation: retrograde cell changes are only present in the nuclei reticulares medius, - superior and - isthmi, following destruction of the ventral funiculus of the spinal cord;
3) from comparison of case 5522 with cases 5516 and 5549 it can be

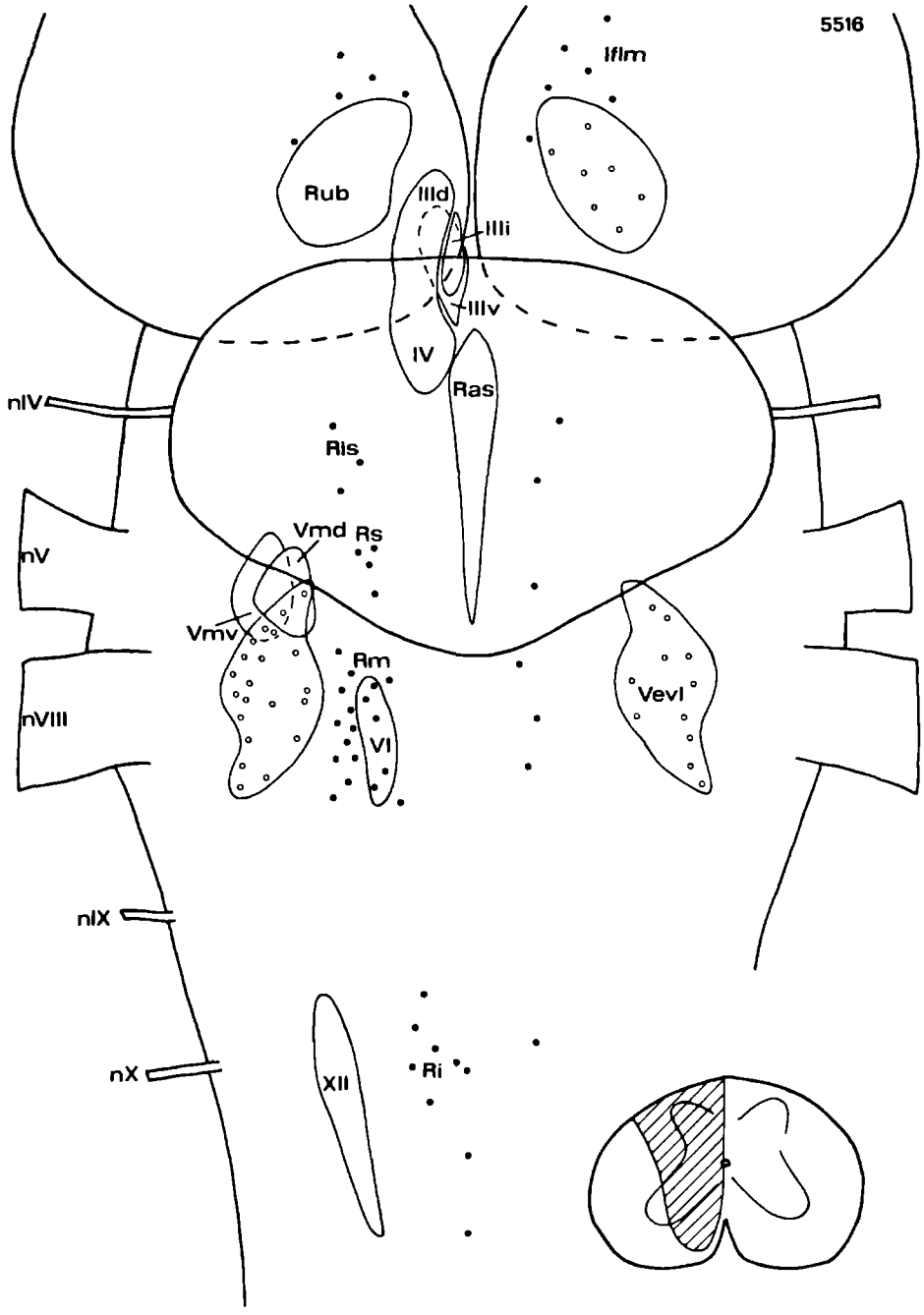


Fig. 38: The distribution of the magnocellular cells in the brain stem of Tupinambis nigropunctatus in which clear-cut retrograde cell changes have been observed, following the spinal cord lesion shown. As filled circles the elements in the reticular formation demonstrating chromatolysis are indicated, about one out of five cells; as open circles the same holds for the ventrolateral vestibular nucleus as well as for the nucleus ruber.

concluded that the only vestibular nucleus showing chromatolytic changes, i.e. the nucleus vestibularis ventrolateralis, sends its axons to the cord via the ventral funiculus, more particularly by way of its medial part;

4) the interstitial nucleus of the f.l.m. shows only chromatolysis when the ventral funiculus, particularly the part dorsal to the anterior commissure, is destroyed (case 5516, 5522);

5) the red nucleus shows clear-cut retrograde cell changes only after lesions involving the most dorsal part of the lateral funiculus (e.g. cases 5516, 5517 and 5519);

6) no retrograde cell changes have been noted in either the nucleus raphes superior or in the tectum mesencephali.

Pseudemys scripta elegans: in tabel 3 the results of two spinal cord hemisections in the turtle Pseudemys are presented. Both are incomplete hemisections: in case 7439 (cf. fig. 39) mainly the lateral funiculus has been destroyed, whereas in case 7438 large part of the lateral funiculus has been spared. In addition one case in Testudo hermanni (7633) is illustrated, which involves part of the contralateral ventral funiculus.

The first two cases clearly illustrate the irreliability of the technique used in respect to the great variability between experiments in the number of chromatolytic cells: in case 7438 in which the ventral funiculus has almost completely been destroyed together with a large part of the lateral funiculus, less neurons do show obvious retrograde cell changes than in case 7439, a lesion of a smaller extent. As already mentioned the Häggqvist material suggests that the main part of descending supraspinal fibres pass via the ventral funiculus.

In these two experiments astonishingly few chromatolytic neurons were found. One might speculate whether this is related only to the irreliability of the technique in question or perhaps also to the absence of trunk musculature.

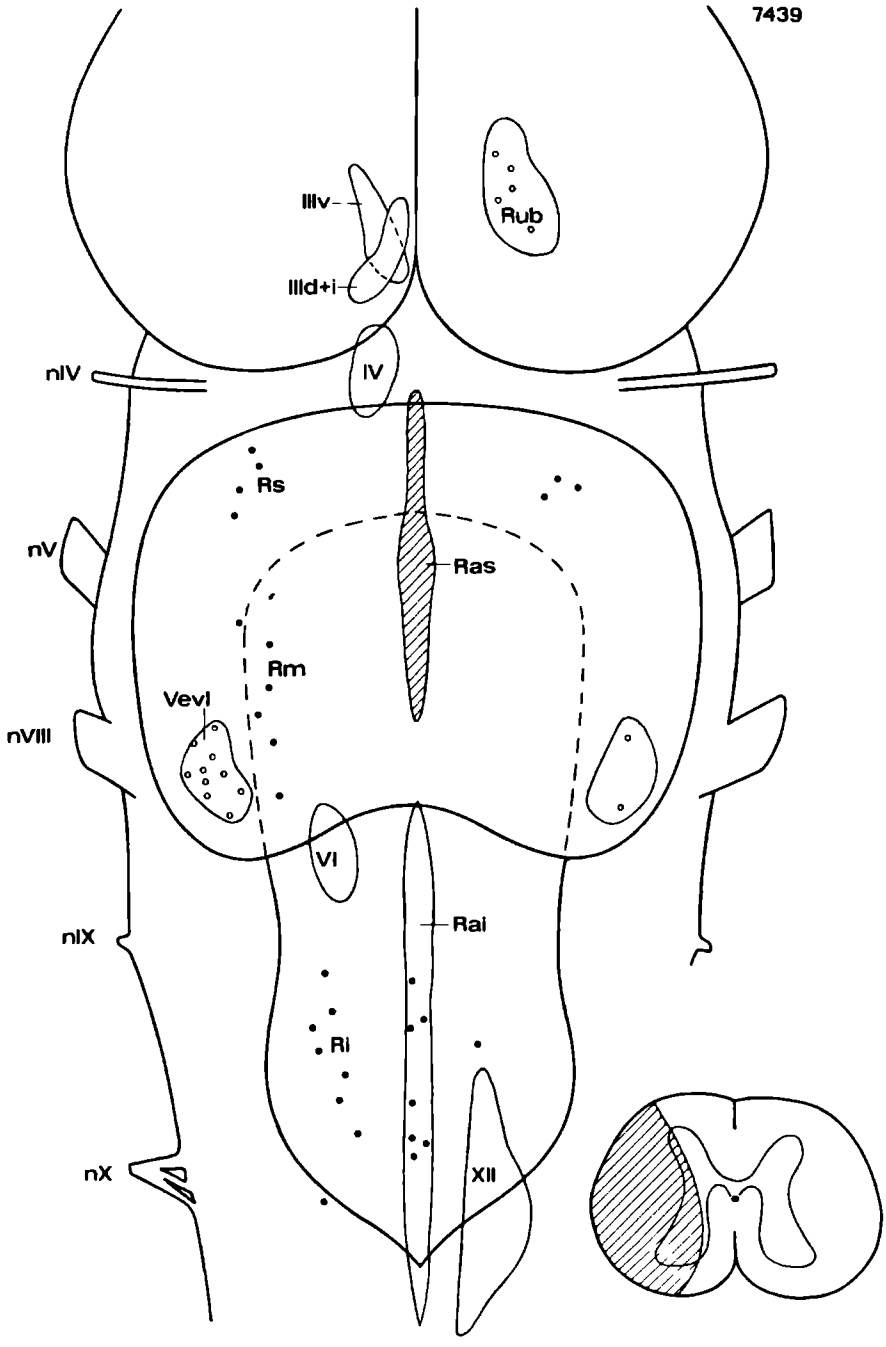


Fig. 39: The distribution of magnocellular cells in the brain stem of Pseudemys scripta elegans, showing retrograde cell changes. For code fcf. fig. 38.

Conclusions:

From the results described above, obtained by studying the ensuing cell changes following spinal cord hemisections, the following conclusions can be drawn:

1) The reticular formation was found to project to the spinal cord in all reptiles studied. Particularly from the results in Python and Tupinambis it can be concluded that the magnocellular rhombencephalic reticular formation can be divided into two parts: a caudal part, comprising the nucleus reticularis inferior, projecting bilaterally to the cord via the lateral funiculus and a rostral part, consisting of the nuclei reticulares medius, - superior, and - isthmi, sending its axons to the spinal cord predominantly ipsilaterally by way of the ventral funiculus. In addition the nucleus raphes inferior projects to the cord.

It is difficult to make quantitative estimates of the neurons projecting to the spinal cord. In the various parts of the reticular formation not more than approximately 30% of the large neurons were involved following high cervical cord lesions. The other magnocellular elements in these areas either do not project to the spinal cord or do not react to severance of their axons.

2) Only one vestibular nucleus reacts to cordotomy with retrograde cell changes, viz., the nucleus vestibularis ventrolateralis - on both sides, implying a bilateral projection.

3) A crossed rubrospinal tract has been demonstrated in the lizard and in the turtle, but not in the Python.

4) The nucleus interstitialis of the f.l.m. has been found to project bilaterally to the spinal cord.

5) No tectospinal tract could be demonstrated in any of the reptiles studied.

b) Labeling of cells in the brain stem following injections of HRP into the spinal cord:

The enzyme horseradish peroxidase (HRP) has been injected into the spinal cord of 8 turtles and 9 lizards. This technique has been used to

gather further information concerning the origin of descending supraspinal systems. It has already been mentioned that analysis of retrograde cell changes has the following serious limitations: 1) following spinal cord lesions more caudally than high thoracic levels no retrograde cell changes could be observed in the brain stem; 2) quantitatively, only few cells respond with distinct cell changes following axotomy. The technique of injecting HRP into the central nervous system has already been employed in reptiles for an analysis of the thalamotelencephalic projections (Lohman, personal communication).

A few notes on the technique in question may be appropriate here. The enzyme horseradish peroxidase applied previously in studies on renal tubular absorption of protein (Strauss, '62) was first employed as a neuroanatomical tool by Kristensson et al.('71) and the LaVails ('72). These investigators proved this enzyme to be transportable (rate of transport 72 mm/day, LaVail and LaVail, '72) in significant amounts in the retrograde direction by axons which terminate near the site of injection rather than by fibres of passage, and without a complicating anterograde transport. Recently, however, some reports have been published in which also the existence of anterograde HRP transport was noted (Kuypers et al., '74; Lynch et al., '74). In the present study only retrograde transport of HRP has been found.

The cells labeled with HRP are clearly visible because of the presence of small brown granules of uniform size, densely stippled, which can be demonstrated following incubation in a medium containing hydrogen peroxide and 3,'3-diaminobenzidine tetrahydrochloride. There is little risk of confusing these granules with background staining of the tissue. However, possible sources of confusion are endothelial cells which take up the protein and red blood cells which have endogenous peroxidase activity (LaVail et al., '73). By light counterstaining with cresylechtviolet these difficulties can be avoided.

In table 4 some of the experiments carried out with this technique are presented. First it was tried to confirm the results obtained in the previous part of this study. Therefore the enzyme has been injected into the cervical intumescence (cases 5538, 5553, 5554). The results

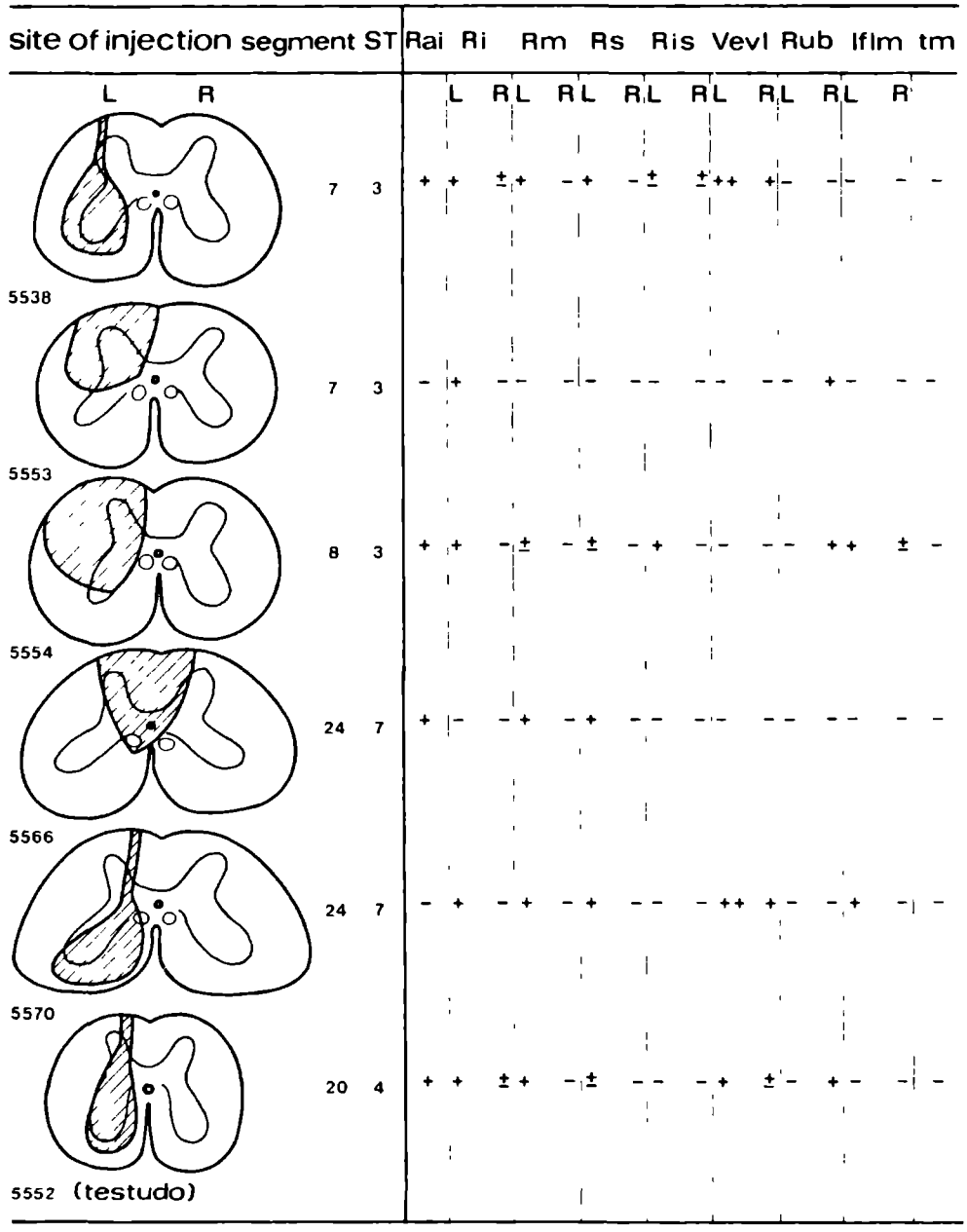


Table 4: Estimates of the number of labeled cells following injection of the enzyme HRP into the cervical and lumbar intumescences in Tupinambis nigropunctatus and in Testudo hermanni (case 5552). The sites of injection are shown as hatchings. For code cf. table 1.

described previously could be confirmed (cf. table 4). No additional cell groups were labeled; e.g. in the tectum mesencephali no labeled cells were found. In these experiments it soon appeared that the quantitative limitations of the technique using retrograde cell changes are even more pronounced following the injection of HRP.

After this pilot study the enzyme has been injected into the lumbar intumescence of the turtle and lizard (cases 5552, 5566 and 5570). These experiments warrant the following conclusion: the descending supraspinal fibre systems extend as far as the lumbar intumescence in the turtle Testudo hermanni (reticulospinal, vestibulospinal and rubrospinal tracts), whereas in the lizard Tupinambis interstitiospinal, reticulospinal and vestibulospinal fibres could be demonstrated. The absence in Tupinambis of labeled cells in the red nucleus may be explained by 'missing' the area of termination of rubrospinal fibres.

c) Discussion:

Reliability of techniques:

The difficulties inherent to the acute retrograde degeneration technique have been discussed by Brodal ('39, '40, '57) and the experiments in this study presented the same problems. There existed a rather great variability between otherwise comparable experiments in the number of chromatolytic cells, particularly in the turtles. In addition not all cells respond retrogradely in the same way, some cells show slighter changes only. An important limitation of the technique in question is the impossibility to obtain results following spinal cord lesions made more caudally than high thoracic in the lizard or in Python at the 42nd spinal segment or more caudally. Similar observations have been made by Beran and Martin ('71) in young opossums. Probably the possibility of finding retrograde cell changes following 'low' lesions of the cord, is reserved only for newborn animals (e.g. kittens). Therefore no attempt can be made to describe any somatotopical arrangement of the fibre systems in question.

It must be stated that the interpretation of negative findings calls for considerable caution. The lack of retrograde cell changes can

never be considered decisive. Nevertheless, before discarding the negative findings as insignificant, it should be realized that particularly large cells in the brain stem react promptly with retrograde changes to the transection of their axons (Pompeiano and Brodal, '57a; Torvik and Brodal, '57). The absence of retrograde cell changes in the Python in the large-celled medial part of the tegmentum mesencephali (in which in other reptiles the red nucleus is found) is therefore not withouth interest.

As regards the HRP experiments it should be pointed out that, until further studies have demonstrated that all axons incorporate and transport HRP, interpretations of results with this relatively new technique should be limited to positive cases (LaVail et al., '73).

The origin of descending fibre systems to the spinal cord:

The results obtained in the present study fit rather well with previous experiments by Robinson ('69) in the lizard Lacerta viridis. This author also described a clear-cut distribution of the neurons of certain parts of the reticular formation into ipsilateral and contralateral groups. In one of his experiments Robinson demonstrated a projection from the interstitial nucleus of the f.l.m. to the spinal cord. As in the present study a bilateral projection from the nucleus vestibularis ventrolateralis was noted. Last not least Robinson was the first author who demonstrated with experimental techniques a crossed rubrospinal pathway in a reptile.

As regards the comparison of the projections from centres in the brain stem to the spinal cord in reptiles with those in mammals, the following similarities can be noted.

The consistent findings in the medial magnocellular zone of the rhombencephalic reticular formation, warrants the conclusion that in this zone two parts can be distinguished: a caudal part, comprising the nucleus reticularis inferior, projecting bilaterally via the lateral funiculus to the spinal cord, and a rostral part consisting of the nuclei reticulares medius, - superior and - isthmi, projecting to the cord predominantly ipsilaterally by way of the ventral funi-

culus. In mammals a similar subdivision into two maximal areas of origin for reticulospinal fibres has been demonstrated (Torvik and Brodal, '57; Beran and Martin, '71), viz., a medullary part comparable with the nucleus reticularis inferior, and a pontine reticular formation which has in common with the reptilian rostral rhombencephalic reticular group a predominantly ipsilateral projection via the ventral funiculus to the spinal cord.

The nucleus raphes inferior of reptiles is not readily comparable with a mammalian cell group, but it should be noted that descending fibres from the raphe nuclei in mammals (Brodal et al., '60) are originating chiefly from the nucleus raphes magnus and descend at least in part via the dorsal half of the lateral funiculus.

In the reptiles studied a bilateral projection from the nucleus vestibularis ventrolateralis to the spinal cord has been shown, confirming Robinson's findings in Lacerta. In mammals, however, following hemicordotomy, retrograde cell changes are present only in the ipsilateral large-celled lateral vestibular nucleus of Deiters (Pompeiano and Brodal, '57a). More recent studies using anterograde degeneration techniques (Nyberg-Hansen, '64; Nyberg-Hansen and Mascitti, '64), however, demonstrated that in mammals also a bilateral projection to the spinal cord in fact exists, arising in the descending and medial vestibular nuclei (for further details see chapter VI).

A crossed rubrospinal tract has been found in the turtles Pseudemys scripta elegans and Testudo hermanni, and in the lizard Tupinambis nigropunctatus. From the various extents of the lesions, especially in the lizard, it is concluded that this tract descends via the most dorsal part of the lateral funiculus. This conclusion is in accordance with our observation in the Häggqvist material. This latter position corresponds to those in the pigeon (Zecha, '61; van den Akker, '69, '70) and in the opossum (Martin and Dom, '70a).

It should be realized, however, that in the opossum the corticospinal tract descends via the dorsal funiculus. In most mammals the corticospinal pathway occupies the most dorsal part of the lateral funiculus, in which case the rubrospinal tract is found ventral to

the latter (cf. Verhaart, '70).

In mammals a small tectospinal tract exists (e.g. Martin, 69a) reaching only cervical levels. The presence of a tectospinal tract in reptiles could not be demonstrated with the retrograde techniques employed. It must be realized, however, that the tectum mesencephali contains rather small cells in which retrograde cell changes are very difficult to detect. Negative findings following the injection of the enzyme HRP into the cord should also be recognized with reservation. Therefore to decide whether a tectospinal tract exists in the reptiles studied surgical lesions have been made in the tectum mesencephali, which will be dealt with in chapter VI of this study.

VI COURSE AND SITE OF TERMINATION OF SUPRASPINAL FIBRE SYSTEMS TO THE SPINAL CORD

The purpose of this part of the present study is to analyse the exact course and site of termination of the descending pathways from the brain stem to the spinal cord. Lesions have been made in those areas which in the previous chapter have been found to project to the spinal cord.

With anterograde techniques the ensuing degeneration has been traced. In order to obtain sufficient data concerning course and site of termination of the descending supraspinal pathways also degenerating fibres have been traced following a high spinal hemisection of the cord.

The techniques used in this study are the silver impregnation procedures according to Nauta-Gygax ('54) and Fink-Heimer ('67), the former for the demonstration of degenerating axons, the latter for the selective impregnation of degenerating terminals. It is now widely recognized that each fibre system studied requires individual attention in order to obtain optimal results with regard to axonal and terminal degeneration. In addition to varying the post-operative survival times, the silver impregnation techniques themselves must often be modified if optimal results are to be achieved (Ebbesson, '70b). In a study about projections from the telencephalon in the lizard Tupinambis nigropunctatus (Lohman and Mentink, '72) post-operative survival times between 12 and 15 days appeared to be optimal for the demonstration of terminal degeneration, whereas for the demonstration of degenerating fibres survival times of at least 3 weeks were necessary. In the turtle comparable post-operative survival times have found to be necessary for optimal results (cf. e.g. Hall and Ebner, '70a, b). For the reptiles used in the present study periods of 2 and 4 weeks have been employed, expected to be appropriate for the demonstration of terminal degeneration respectively degenerating fibres.

After this introduction the descending supraspinal fibre systems will be described in the following order:
a) descending fibres following a high hemisection of the spinal cord; b) descending projections from the tectum mesencephali; c) rubrospinal

projections; d) vestibulospinal projections, and e) descending pathways via the fasciculus longitudinalis medialis, i.e., interstitiospinal and reticulospinal tracts.

A comparison with experimental data found in mammals, especially the opossum and the cat, will be made following each section.

a) Descending fibres following a high hemisection of the spinal cord:

In order to establish the total distribution of the descending tracts from the brain stem to spinal cord, the degeneration ensuing high cervical hemicordotomies has been studied. The brain stems of the specimens which sustained these lesions have been employed to study the ensuing retrograde cell changes (cf. table 1-3, chapter V).

Figure 40 illustrates the results obtained in one representative experiment in each of the three reptiles studied. The observations made are presented in this figure in transverse sections of representative spinal cord segments, viz., sections through the cervical and lumbar intumescences completed with a thoracal section in the turtle and lizard, whereas in the snake the 25th, 100th (about in the middle of this animal) and 210th (directly precloacal) spinal segments have been chosen.

The lesions shown involve a small part of the opposite side, viz., part of the dorsal and ventral funiculi. Cases in which the opposite side was not involved, revealed that this extension hardly influences the descending degeneration on the side of the lesion, viz., only a few crossing fibres have been noted in or caudal to the first spinal segments.

Descending degenerating fibres have been found mainly in the lateral and ventral funiculi. The very few descending degenerating fibres coursing caudally in the funiculus dorsalis appeared to descend only over a short distance. Maximal intensity of degenerating fibres is found immediately below the lesion.

In Tupinambis (case 5551) the lesion involves contralaterally the medial part of the ventral funiculus and the entire dorsal funiculus.

In the lateral funiculus degenerating fibres were found to descend

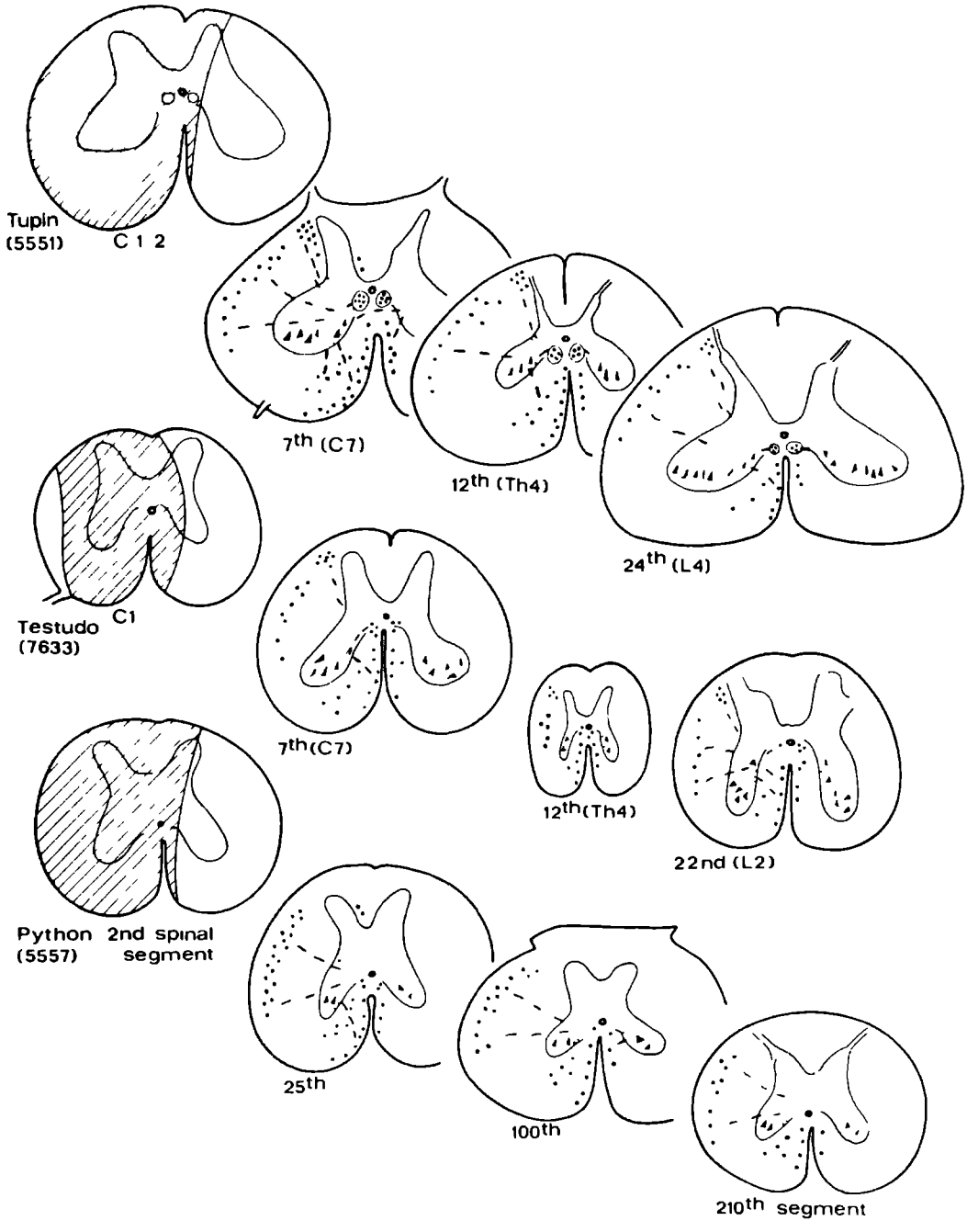


Fig. 40: Degeneration following a high hemicordotomy in Tupinambis nigropunctatus, Testudo hermanni and Python reticulatus. In this as well as in the figures 41-43 and 45 hatchings indicate the position and extent of the lesion, coarse dots and broken lines transversally respectively longitudinally cut degenerating fibres, whereas small dots represent evidence of preterminal degeneration. The motoneurons in the spinal cord are also shown.

in two pathways: 1) in a rather distinct bundle in its most dorsal part, close to the dorsal root, and 2) in a more diffusely organized system found along the periphery of the lateral funiculus. Both bundles extend throughout the spinal cord and diminish caudalward.

From the first bundle fibres could be traced to the so-called intermediate zone in the spinal gray matter (cf. fig. 40). Preterminal degeneration in this zone was most extensive in the cervical and lumbar enlargments. This bundle is identical with the rubrospinal tract found in the Häggqvist preparations. The bundle in question could be traced in the spinal cord as far as the lumbar intumescence.

Fibres issuing from the second, more ventrally located system could be traced medially, passing just dorsal to the lateral column of motoneurons (in the intumescences) to the medial part of the ventral horn. The latter contains a pool of termination in which degenerating fibres from the lateral as well as from the ventral funiculus participate. A few fibres originating from the contralateral side probably also terminate here, passing via the anterior as well as the posterior commissure.

The ventral funiculus contains the bulk of the descending systems to the spinal cord. The following subdivision of the fibre degeneration as present in the ventral funiculus can be made:

1) a system of degenerating fibres, forming a thin layer in the superficial zone which, as it descends caudalward, shifts to a more dorsomedial position;

2) a more diffusely organized fibre system, situated between the former and the ventral horn, and

3) a small compact, dorsal bundle of degenerating fibres separated from the main part of the ventral funiculus by the anterior commissure.

From these three systems degenerating fibres could be traced to the medial pool of termination referred to above. Almost no fibres were found to terminate in the lateral column of motoneurons. Only a few degenerating fibres decussate toward the opposite side of the gray matter. These crossing fibres pass via both the anterior and the posterior commissures.

Due to the involvement of the medial part of the ventral funiculus opposite to the lesion, only part of the superficially situated system and the small dorsal bundle could be traced.

In the turtle Testudo hermanni exactly the same descending fibre tracts could be traced as far as the lumbar intumescence as in the lizard Tupinambis. These tracts show the same course through the spinal cord and terminate also in two particular sites in the gray matter, viz. in the intermediate zone and in the medial part of the ventral horn. The lateral column of motoneurons has been spared again.

The findings in the Python are readily comparable to the above results, however, with one notable exception. The bundle of degenerating fibres concentrated in the turtle and lizard in the most dorsal part of the lateral funiculus could not be demonstrated in the Python. In accordance to the absence of this system of degenerating fibres no termination has been observed in the intermediate zone. The degenerating fibres demonstrated in Python were found to terminate mainly in the ventral part of the ventral horn, whereas some fibres terminate in the area adjoining to the central canal. The more stronger density of degeneration found in Python in the lateral funiculus, representing degenerating reticulospinal fibres as shown in chapter V of this study, should also be mentioned.

Discussion:

Comparing the degeneration traced in cases of on the one hand the lizard and the turtle, and on the other hand the snake, the apparent absence of a fibre system passing via the most dorsal part of the lateral funiculus in Python is the most striking difference. It has already been mentioned that this tract is found in a position occupied in the Häggqvist preparations of Tupinambis by the rubrospinal tract. Other evidence that the rubrospinal tract in the lizard descends in the most dorsal part of the lateral funiculus has been presented in chapter V dealing with retrograde cell changes following spinal cord lesions.

With regard to the other descending fibre systems the results obtained in the three reptiles studied are largely comparable.

By combination of the data obtained from 1) the fibre systems demonstrated to descend to the spinal cord in the Häggqvist material (chapter III) and 2) the results obtained in studying retrograde cell changes following spinal cord lesions (chapter V), it seems likely that:
- the diffuse fibre system found descending in the lateral funiculus consists of reticulospinal fibres arising in the inferior reticular nucleus and probably also in the nucleus raphes inferior; this system is particularly well developed in Python;
- the superficial system of degenerating fibres in the ventral funiculus consists of vestibulospinal fibres;
- the more diffusely arranged fibres in the ventral funiculus have their origin in the rostral part of the rhombencephalic reticular formation;
- the small bundle separated from the remainder of the ventral funiculus by the anterior commissure most probably contains interstitiospinal fibres.

Further evidence for these somewhat tentative conclusions will be presented in the following sections of this chapter, which are concerned with the individual fibre tracts.

The absence of degenerating fibres and of preterminal degeneration in the lateral column of motoneurons should be interpreted with caution, because of the enormous extent and overlap of the dendritic trees of the motoneurons in the reptilian spinal cord. In mammals a direct termination of descending supraspinal fibre systems on such motoneurons exists primarily in primates: it is lacking in the cat, but is present in increasing numbers in the monkey, the chimpanzee and man (Kuypers, '64). Recently, a direct corticospinal projection to the lateral column of motoneurons has been shown in the raccoon, a non-primate with very detailed finger movements (Petras, '68, '69; Wirth et al., '74). Golgi studies in kittens have demonstrated the presence of a considerable extent of the dendritic trees of the lateral column of motoneurons into the medial zone of internuncial cells (Scheibel and Scheibel, '66).

b) Descending projections from the tectum mesencephali:

Surgical ablations of the tectum mesencephali have been made in 6 turtles (2 of the species Testudo hermanni, 4 Pseudemys scripta elegans), 2 snakes (Python reticulatus) and 10 lizards (Tupinambis nigropunctatus). These experiments have been carried out to analyse via which pathways the tectum may influence the spinal cord, since stimulation experiments in reptiles (Bagley and Langworthy, '26; ten Cate, '37; Goodman and Simpson, '60; Shapiro and Goodman, '69) have shown that the tectum mesencephali exerts influence over the spinal cord. These authors did not make pertinent statements whether these effects are direct or indirect, the latter e.g. via the reticular formation. In the retrograde studies presented in chapter V no positive evidence has been found for a direct tectospinal projection, comparable to that in mammals, e.g. in the opossum (Martin, '69a) or in the cat (Nyberg-Hansen, '66).

Since only very small differences have been noted between the results following tectal ablations in the various reptiles studied, it will be sufficient to describe these projections for the lizard Tupinambis (illustrated in figure 41). Differences found in other reptiles studied will be mentioned when necessary.

Following a large lesion including all six tectal layers degenerating fibres have been noted in various systems: 1) an ascending projection to pretectal and thalamic regions; 2) a commissural component to the opposite tectal hemisphere, some fibres could be traced to the contralateral tegmentum mesencephali, and 3) a descending projection which can be subdivided into two main descending pathways, one crossed, the other remaining ipsilateral. In addition, a rather diffuse tectotegmental system has been found, which appeared to be related to the mesencephalic part of the reticular formation.

The degeneration in the tectum mesencephali itself is restricted largely to the stratum griseum centrale and stratum album centrale. Much less degenerating fibres are found in the stratum griseum periventriculare. From the latter a periventricular fibre system arises bringing probably the tectum mesencephali into relation with the torus

semicircularis and with the periaqueductal gray. In the superficial layers of the tectum mesencephali degenerating fibres can be traced over only a short distance.

As regards the ascending projections of the tectum mesencephali only a few remarks will be made within the frame of this study. Following a large lesion, degenerating fibres could be traced to the ipsilateral nucleus rotundus, the ventral part of the nucleus geniculatus lateralis and a few fibres also to the nucleus dorsomedialis thalami. In the pretectum fibres are given off to the nucleus geniculatus pretectalis and to the nucleus lentiformis mesencephali.

Contralateral thalamic nuclei also receive fibres from the tectum mesencephali, viz., the nucleus rotundus and the ventral part of the nucleus geniculatus lateralis. These fibres reach their site of termination by way of the supraoptic decussation.

These results are in harmony with the experimental findings in other reptiles (Ebbesson, '70a; Hall and Ebner, '70a; Butler and Northcutt, '71; Braford, '72; Foster et al., '73).

In a few cases in which the lesion extended into the torus semicircularis, degenerating fibres could be traced to the ipsilateral nucleus reuniens, confirming for Tupinambis (and Testudo hermanni) the projection described in Caiman (Pritz, '74) and in the lizard Iguana (Foster, '74).

With regard to the descending projections of the tectum mesencephali it has already been mentioned that, following a large tectal lesion, degenerating fibres assemble in two main descending pathways, one crossed, the other remaining ipsilateral.

The ipsilateral descending pathway, i.e., the tractus tectobulbaris ventralis (s. lateralis), passes downwards through the nucleus profundus mesencephali. In the latter some preterminal degeneration has been noted. The lateral tectobulbar tract continues caudalward into the direction of the nucleus isthmi. The nucleus isthmi, particularly its magnocellular part (cf. fig. 41) receives an important projection from this pathway. In the isthmic area a few degenerating fibres are also given off to the nucleus reticularis

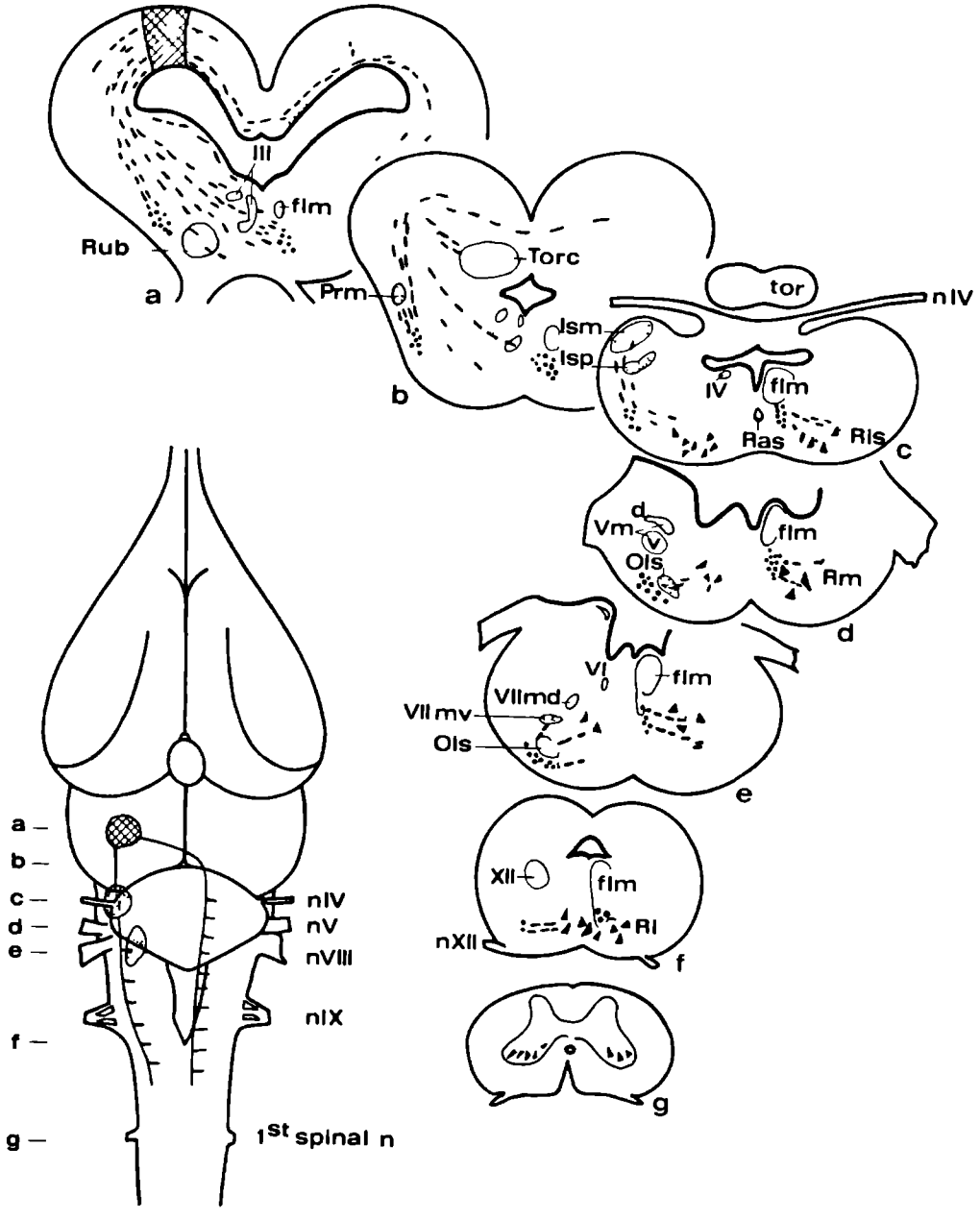


Fig. 41 A series of transverse sections through the brain stem and through the first spinal segment in the lizard Tupinambis nigropunctatus subjected to a lesion destroying part of the tectum mesencephali. For symbols cf. fig. 40. In addition the course and termination of the descending pathways from the tectum are indicated in a dorsal view of the brain of Tupinambis.

isthmi. Descending along the ventrolateral surface of the brain stem, the ipsilateral tectobulbar tract also sends fibres into the more lateral part of the remaining portions of the rostral reticular formation. It passes through the oliva superior in which preterminal degeneration has been found. In Fink-Heimer sections in the turtle also terminal degeneration has been noted in this nucleus. In addition, a few fibres could be traced to the ventral part of the facial motor nucleus. In the turtle this ipsilateral tectobulbar tract could not be traced further caudally as the oliva superior. In the lizard and the snake, however, the tract in question descends as far as the level of the hypoglossal nucleus. Degenerating fibres are send to the more lateral part of the nucleus reticularis inferior.

An appreciable amount of degeneration in this ipsilateral tectobulbar pathway has been found only following lesions extending at least as far as the stratum griseum centrale.

The contralateral descending pathway is the continuation of the dorsal tectobulbar tract, which decussates in the tegmentum mesencephali. This predorsal bundle can be traced as far caudally as the ipsilateral tract, viz., as far as the hypoglossal nucleus. At this level the bundle of degenerating fibres fans out. In the lizard this bundle could be traced only in one series into the first spinal segment. During its caudal course the predorsal bundle discharges fibres at right angles to the various parts of the medial, magnocellular reticular zone, and in addition to the nucleus raphes inferior. Preterminal degeneration has been noted only contralateral to the lesion, i.e. on the side of the degenerating fasciculus predorsalis. In addition a few fibres could be traced to the oliva superior.

Discussion:

As regards the descending projections of the tectum mesencephali two pathways have been demonstrated in the reptiles studied: an ipsilateral pathway projecting to the nucleus isthmi, the oliva superior, the ventral part of the facial motor nucleus and particularly to the

more lateral parts of the reticular formation. The crossed fasciculus predorsalis on the other hand, projects to the medial part of the reticular formation. A tectospinal tract of any importance could not be demonstrated.

In mammals, e.g. the opossum, the superior colliculus projects to the ipsilateral part of the brain stem via a tectobulbar and a tectopontine bundle and to the contralateral part of the brain stem by way of the predorsal bundle (Martin, '69a; Rafols and Matzke, '70). The ipsilateral tectobulbar bundle projects to the mesencephalic, pontine and medullary parts of the reticular formation, to the motor nucleus of the facial nerve and in addition to the inferior olivary complex and to the pontine nuclei. In reptiles neither an oliva inferior nor pontine nuclei could be demonstrated in normal material (Ariëns Kappers et al., '36; ten Donkelaar and Nieuwenhuys, '75). The present experimental material has not provided evidence for particular sites of termination, which may foreshadow a primordial oliva inferior or pontine nuclei. It should also be noted that no direct tectocerebellar fibres could be demonstrated as described in normal material (Ariëns Kappers et al., '36).

A tectal projection to the oliva superior has been found in the reptiles studied. A similar observation has been made in the frog (Rubinson, '68). In the opossum (Martin, '69a) as well as in the monkey (Moore and Goldberg, '66) following a lesion of the inferior colliculus a small projection has been shown to the medial part of the superior olive. Following lesions involving part of the torus semicircularis, i.e. the reptilian primordium of the inferior colliculus, no additional degenerating fibres could be traced to the superior olive.

The projection from the tectum mesencephali to the superior olive relates the latter nucleus to visual function (Rubinson, '68). A similar relation has been suggested on the basis of comparative studies in diurnal and nocturnal mammals (Harrison and Irving, '66). In the former the medial superior olive is particularly large, whereas in nocturnal forms this nucleus is almost or even completely absent.

Finally, the important question as to how the tectum mesencephali influences the spinal cord, should be discussed. In the lizard only a few fibres from the fasciculus predorsalis could be traced to the first spinal segement. Hence, it is likely that the tectum mesencephali influences the spinal cord almost entirely indirectly, viz., via its projection to the reticular formation.

c) Rubrospinal projections:

So far experiments aiming to destroy, either surgically or electrolytically, the red nucleus in the turtle Testudo hermanni and the snake Python reticulatus have failed to produce specific lesions. In 4 out of 10 experiments performed in the lizard Tupinambis nigropunctatus, however, it has been possible to place discrete lesions in the nucleus ruber. Such a lesion invariably interrupted the descending projections of the tectum mesencephali and also passed through the torus semicircularis. One of these experiments is presented in figure 42. In this experiment, in which a lesion destroyed almost the entire red nucleus, a discrete bundle of descending degenerating fibres has been demonstrated. This bundle decussates almost immediately, shifts toward a dorsal direction along the periphery of the tegmentum mesencephali and finally takes a position just medial to the descending tract of the trigeminal nerve. This tract corresponds to the rubrospinal tract, demonstrated in the Häggqvist preparations of Tupinambis.

The degeneration traced caudalward was not only due to the lesion in the red nucleus, but in addition, was also due to the involvement of the tectum mesencephali, the mesencephalic part of the reticular formation and to the interruption of passing fibres.

The rubrospinal tract pursued a course through the brain stem similar to that illustrated in chapter III (cf. figs. 13-21). At caudal levels of the brain stem the rubrospinal tract shifts dorsally from its lateral position. Finally it takes a position in the most dorsal part of the lateral funiculus of the spinal cord. On its course through the brain stem degenerating fibres leave the rubrospinal tract and can be traced to the nucleus cerebelli lateralis, to the various nuclei

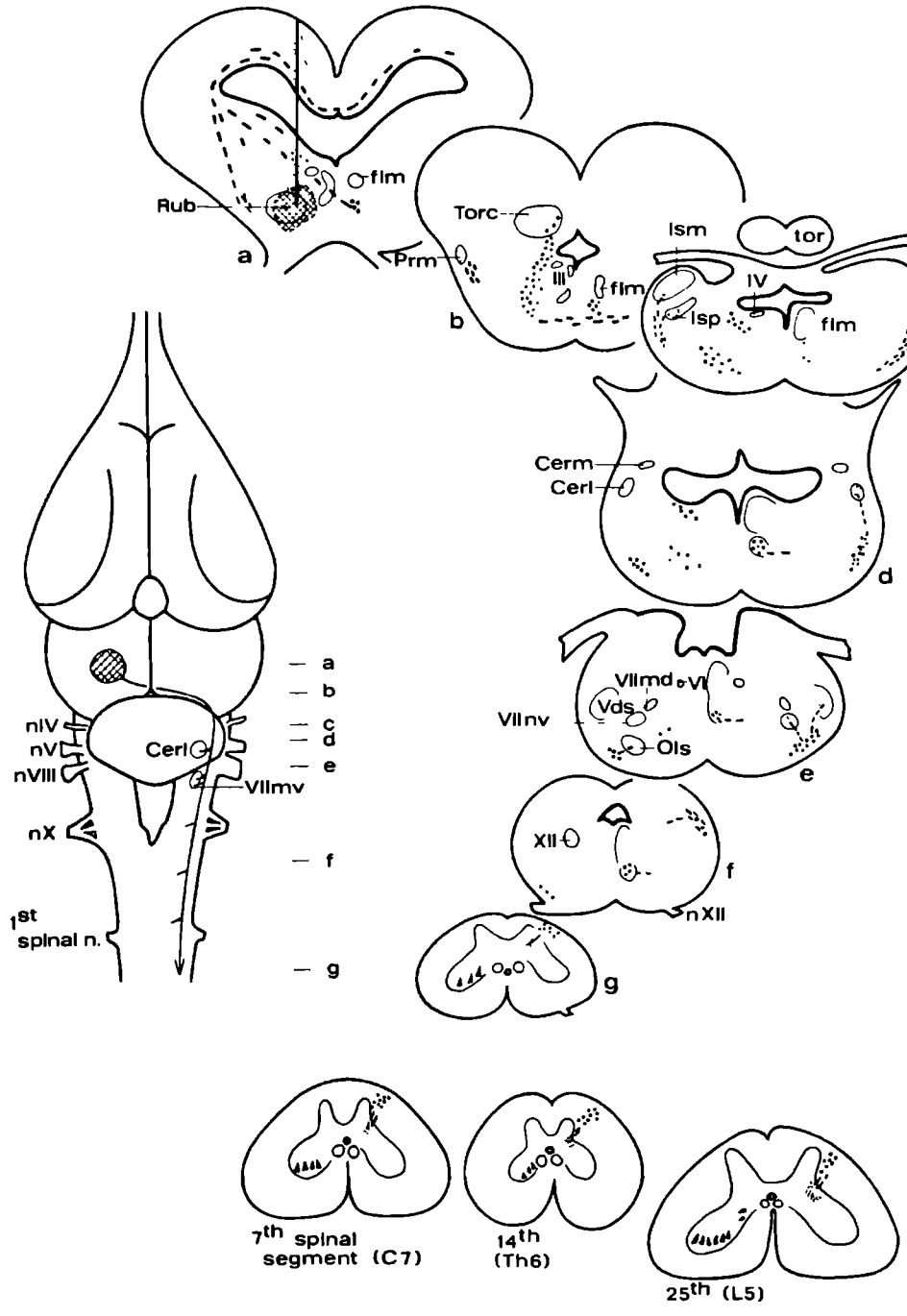


Fig. 42: A series of transverse sections through the brain stem and through representative levels of the spinal cord in Tupinambis nigropunctatus illustrating the ensuing anterograde degeneration following a lesion within the red nucleus. For symbols cf. fig. 40. The course of the rubrospinal tract through the brain stem is also shown in a dorsal view of the brain.

belonging to the trigeminal nerve: the nucleus princeps, the nucleus descendens and the nucleus motorius n. trigemini. Profuse preterminal degeneration has also been noted in the ventral part of the nucleus motorius n. facialis. More caudally degenerating fibres from the rubrospinal tract can be followed to the parvocellular lateral part of the reticular formation.

The rubrospinal tract remains throughout the spinal cord situated in the most dorsal part of the lateral funiculus. From this position fibres can be traced to the intermediate zone, in which preterminal degeneration has been observed. The termination was most extensive within the cervical and lumbar enlargements. No fibres could be traced to either the dorsal or the ventral horn.

Following lesions in the red nucleus in which only its dorsomedial part has been destroyed, only a few degenerating fibres could be traced to the cervical enlargement and not to the more caudal parts of the spinal cord. These results suggest a somatotopical arrangement of the rubrospinal projection, comparable to that in cat (Pompeiano and Brodal, '57c).

Descending ipsilateral degeneration was limited to the ipsilateral tectobulbar tract and to a rather diffuse fibre system remaining periventricularly and related particularly to the griseum centrale. In addition a few scattered fibres could be traced in a more ventral position as far as the level of the nucleus abducens (cf. fig. 42).

Ascending degeneration could be followed as a rather diffuse fibre system to the ventral thalamus. This system probably includes fibres from the mesencephalic part of the reticular formation and the brachium conjunctivum. Hence, no pertinent statements can be made whether ascending fibres arise in the red nucleus or not. Experimental work in mammals (Edwards, '72; Hopkins and Lawrence, '73, '75) indicates that there is no appreciable ascending projection from the red nucleus.

Discussion:

In Tupinambis as well as in Testudo a rubrospinal tract has been found. This system decussates in the tegmentum mesencephali, descends

in the most dorsal part of the lateral funiculus and terminates in the intermediate zone of the spinal gray matter. Neither from our retrograde nor from anterograde studies experimental evidence could be gathered for the existence of a rubrospinal tract in Python.

Comparing the rubrobulbar projections in the lizard Tupinambis with the corresponding projection in the opossum (Martin and Dom, '70b; Martin et al., '74) the following similarities can be noted: in both vertebrates projections of the red nucleus have been demonstrated to various parts of the trigeminal nerve nuclei, to the motor nucleus of the facial nerve, to the lateral (parvocellular) part of the reticular formation and to the deep cerebellar nuclei (in the opossum to the interpositus complex).

No ipsilateral rubrobulbar projection could be demonstrated in Tupinambis. In mammals such a pathway has been shown experimentally to be related to the inferior olive (Walberg, '56; Hinman and Carpenter, '59; Edwards, '72). In the opossum, however, such a pathway is not conclusively shown (Martin et al., '74).

Evidence has been presented for a crossed rubrospinal tract in the lizard Tupinambis nigropunctatus and also in the turtle Testudo hermanni. As regards course and mode of termination this tract is comparable to the rubrospinal system in mammals (e.g. cat - Nyberg-Hansen and Brodal, '64; opossum - Martin and Dom, '70a; Martin et al., '74; rat - Waldron and Gwyn, '69; Brown, '74). In these mammalian species the rubrospinal tract terminates mainly in the laminae VI and VII of Rexed ('52, '54). As regards their position these layers roughly correspond to the intermediate zone of reptiles.

d) Vestibulospinal projections:

In 7 turtles (Testudo hermanni), 2 snakes (Python reticulatus) and 5 lizards (Tupinambis nigropunctatus) surgical lesions were placed in the vestibular nuclear complex. In the lizard the vestibular area is largely covered by the internal ear and therefore rather difficult to approach. So far only a small part of the vestibular nuclear complex has been destroyed in an experiment, aimed to inflict a lesion to the

nucleus reticularis medius (cf. fig. 44). The degenerating fibres traced in this experiment pass by way of the lateral vestibulospinal tract. In the turtle and the snake considerable part of the vestibular nuclear complex has been destroyed, but it has not been possible to place selective lesions in the individual vestibular nuclei. In chapter V it has been demonstrated that the nucleus vestibularis ventrolateralis is the only vestibular nucleus showing retrograde cell changes following spinal cord lesions. This finding, however, does not rule out the possibility that also other vestibular nuclei contribute to the vestibulospinal projections.

In most experiments carried out only slight postural changes were observed, in 2 turtles tilting of the head to the side of the lesion has been noted, but no obvious extension of the contralateral limbs as reported in the toad (Barale et al., '71) or in the cat (Pompeiano, '72) has been found.

The lesions invariably also involved the acoustic area, which is situated dorsal to the vestibular nuclear complex. This involvement produced degenerating fibres which descend to the floor of the brain stem, cross the midline and ascend as the lateral lemniscus to the torus semicircularis. This finding confirms a projection from the acoustic nuclei to the contralateral torus semicircularis as demonstrated by Foster ('74) in the lizard Iguana iguana.

Additional ascending degeneration could be traced bilaterally via the fasciculus longitudinalis medialis (f.l.m.) to the nuclei which innervate the extraocular musculature (IV and III). This ascending pathway which is mainly ipsilateral will be discussed further in the following section dealing with the various components of the f.l.m.

Before describing the descending degeneration a commissural component to the opposite vestibular nuclear complex, a bilateral projection to the nucleus abducens and a small projection to the cerebellum (stratum granulare) should be mentioned.

In figure 43 two of the experiments carried out are illustrated, at the left a representative case in the turtle Testudo hermanni, at the right one in Python. Descending degeneration has been found throughout

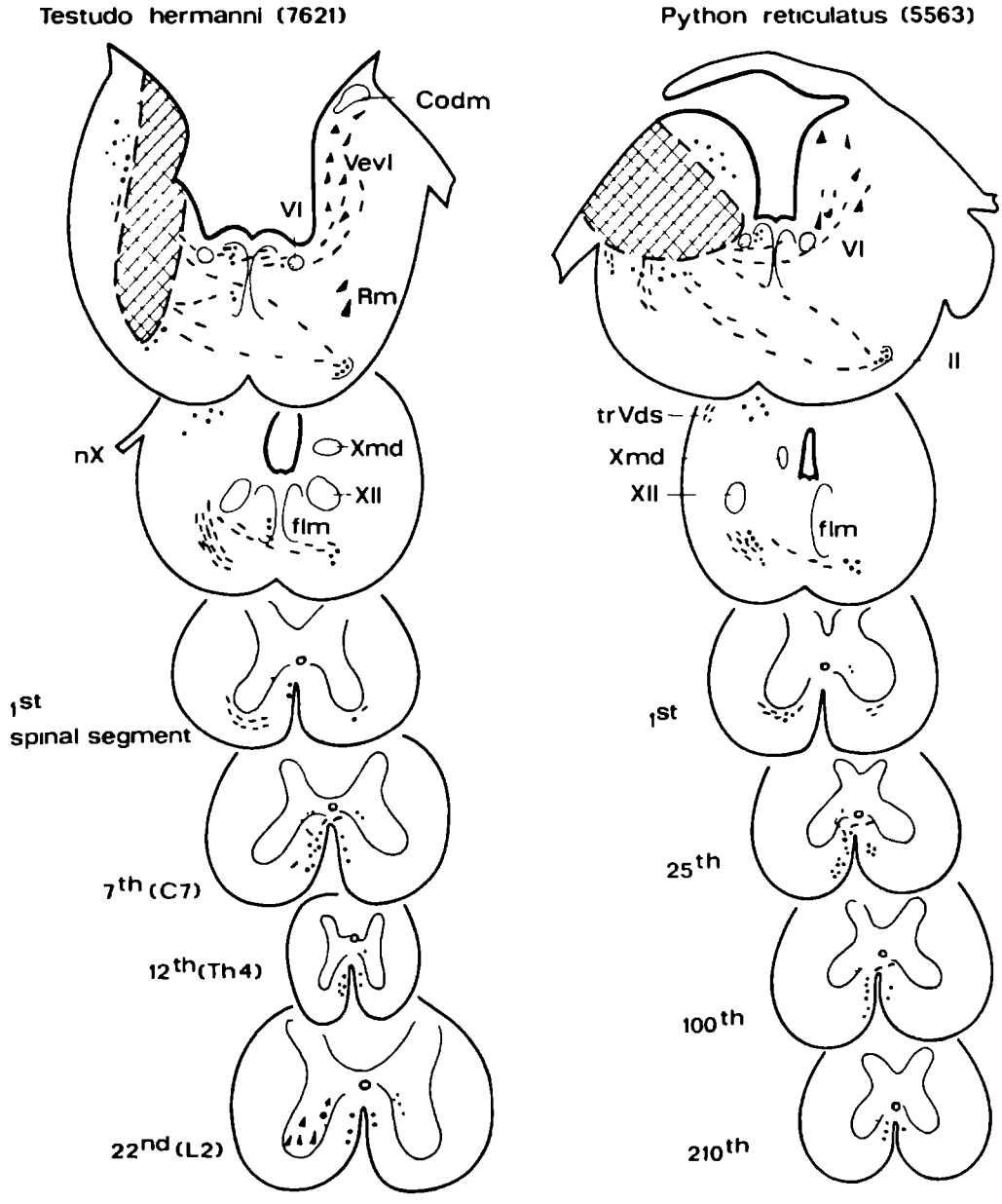


Fig. 43: A diagrammatic representation of the course and distribution of degenerating fibres within the brain stem and spinal cord following a lesion involving the vestibular nuclear complex, at the left in Testudo hermanni, and at the right in Python reticulatus. For symbols cf. fig. 40.

the brain stem and spinal cord as far as the lumbar intumescence in the turtle (and lizard, cf. fig. 44) and as far as precloacal spinal segments in Python. It could be traced as a conspicuous bundle of degenerating fibres taking a course through the brain stem similar to that observed in the Häggqvist preparations for the lateral vestibulospinal tract. During its caudal course this bundle of degenerating fibres gradually shifts ventromedialward, turns around the ventral horn of the spinal gray, and finally attains a superficial position in the ventral funiculus. In this position it can be traced further caudalward. Fibres are given off to the medial part of the ventral horn. This bundle is much better developed in the turtle than in the snake. In the turtle terminal degeneration has been noted in the medial part of the ventral horn following a survival time of two weeks (Fink-Heimer preparations).

This vestibulospinal projection is not exclusively ipsilateral as in mammals (Nyberg-Hansen and Mascitti, '64). In the most caudal part of the brain stem some fibres appear to cross the midline and descend via the opposite ventral funiculus of the spinal cord. In the cord itself also a few fibres were found to cross, just ventral to the central canal by way of the anterior commissure.

In the reptiles studied no medial vestibulospinal tract by way of the fasciculus longitudinalis medialis as suggested by the Häggqvist preparations could be demonstrated. In the turtle (fig. 43) a few degenerating fibres passed by way of the f.l.m. to the spinal cord. However, this is probably due to the involvement of the nucleus reticularis medius.

Discussion:

In the three reptiles studied the course and mode of termination of the vestibulospinal projection have been investigated. In addition to this descending pathway ascending fibres have also been demonstrated. These ascending projections of the vestibular nuclear complex, passing by way of the f.l.m., are basically comparable to those in mammals: a bilateral (predominantly ipsilateral) projection to the nuclei III, IV and VI (cf. e.g. cat: Carpenter and Hanna, '62; Tarlov, '70, '72;

monkey: Carpenter and Strominger, '65; McMasters et al., '66; Carpenter, '71).

As regards the descending projections of the vestibular nuclear complex a vestibulospinal pathway could be demonstrated identical to the lateral vestibulospinal tract found in the Häggqvist preparations and similar to the system of degenerating fibres, situated as a thin layer in the superficial zone of the ventral funiculus following high cervival hemicordotomies (cf. fig. 40). A medial vestibulospinal tract passing via the f.l.m. as present in the cat (Nyberg-Hansen, '64) could not be demonstrated.

In contrast with the purely ipsilateral lateral vestibulospinal tract in the cat (Nyberg-Hansen and Mascitti, '64), the vestibulospinal tract in reptiles as in amphibians (Corvaja and Grofová, '72; Corvaja et al., '73; Fuller, '74) partly decussates in the caudal part of the brain stem. This explains why, following a hemisection of the spinal cord the ventrolateral vestibular nucleus in reptiles shows bilaterally retrograde cell changes. In the cat there is no anatomical evidence that lateral vestibulospinal fibres cross within the spinal cord (Pompeiano, '72), whereas in the reptiles studied a few fibres were found to decussate, just ventral to the central canal by way of the anterior commissure.

It has been indicated before that in the cat two vestibulospinal pathways have been demonstrated, viz., an ipsilateral one, arising in the lateral vestibular nucleus (Nyberg-Hansen and Mascitti, '64) and a very modestly developed bilateral projecting medial vestibulospinal pathway, originating mainly form the medial vestibular nucleus (Nyberg-Hansen, '64).

It seems possible that vestibular influence over the spinal cord in reptiles as well as in amphibians is carried out by only one tract, viz., the bilaterally projecting vestibulospinal tract. In mammals, however, two pathways are present, probably allowing a more precise control over the motor centres in the spinal cord.

e) Descending pathways via the fasciculus longitudinalis medialis: interstitiospinal and reticulospinal tracts:

The fasciculus longitudinalis medialis (f.l.m.) represents one of the oldest fibre systems in vertebrates (Ariëns Kappers et al., '36). In mammals it is customary to consider the f.l.m. in connexion with the secondary vestibular tracts (Brodal et al., '62). It should be emphasized, however, that interstitiospinal and reticulospinal fibres constitute important additional components of the f.l.m. (Busch, '61). The analysis of Häggqvist preparations in the present study (chapter III) indicated that the same holds true for the f.l.m. in the reptiles studied. These components, originating from the nucleus interstitialis of the f.l.m. and from the rostral part of the magnocellular reticular formation (nuclei reticulares isthmi, - superior and - medius), could be traced in favourable sections over considerable distances caudalward in the Häggqvist preparations (cf. e.g. figs. 16-18). However, because of intermingling, the various components of the f.l.m. could not be traced as individual entities to the spinal cord. In addition to interstitiospinal and reticulospinal fibres the possibility of the presence of vestibulospinal fibres, passing via the f.l.m., should also be considered. The latter pathway could not be confirmed in the previous section of the present study dealing with the vestibulospinal projections.

This section is concerned with the various components of the f.l.m. In Tupinambis surgical lesions have been placed within the region of, respectively, the nucleus interstitialis of the f.l.m., the nucleus reticularis superior and the nucleus reticularis medius. In figure 44 the lesions in the nuclei mentioned are represented in order to illustrate in which part of the f.l.m. the descending fibres of these nuclei can be found. The lesion in the nucleus reticularis medius also destroyed efferent fibres from the vestibular nuclear complex, ascending via the f.l.m., as well as descending fibres. The latter form part of the tractus vestibulospinalis lateralis.

Following the lesion just rostral to the red nucleus in which part of the nucleus interstitialis of the f.l.m. has been destroyed,

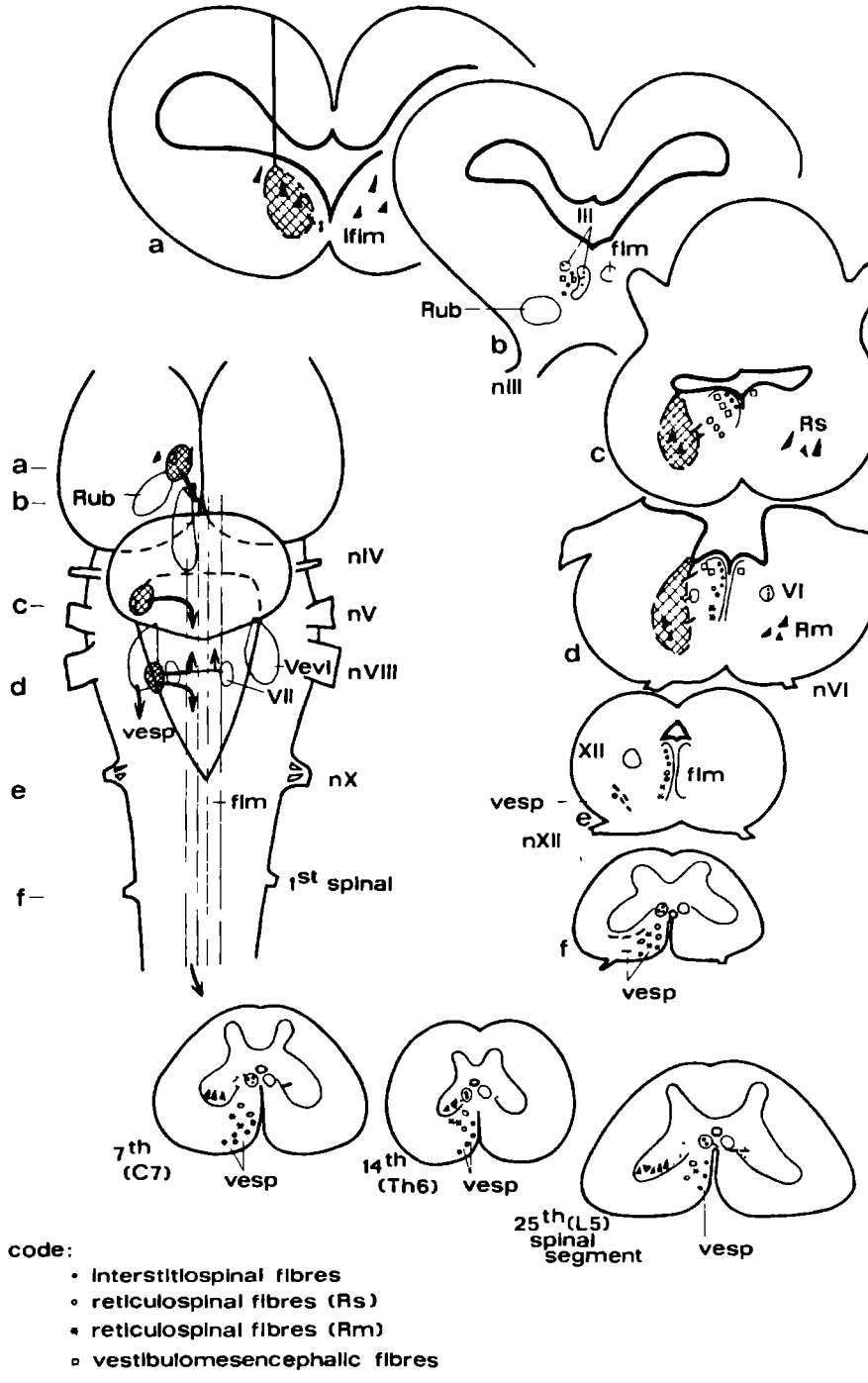


Fig. 44: Dorsal view of the brain stem of Tupinambis nigropunctatus in which three lesions are shown giving rise to degenerating fibres passing via the f.l.m. In a series of transverse sections the arrangement of the various ascending and descending fibre components of the f.l.m. is shown.

interstitiospinal fibres can be traced to the dorsomedial part of the f.l.m. Gradually they shift into a more ventral position close to the midline. In the spinal cord they can be found as a distinct bundle which is separated from the main part of the ventral funiculus by the anterior commissure.

Reticulospinal fibres arising in the nucleus reticularis superior can be traced to the lateral part of the f.l.m. Soon these fibres take a position ventral to the interstitiospinal fibres.

Degenerating fibres following a lesion in the nucleus reticularis medius can also be traced to the f.l.m., where they finally take a place just ventral to the reticulospinal fibres originating from the nucleus reticularis superior. In the spinal cord the descending fibres from both reticular nuclei intermingle.

All of these fibre systems appeared to terminate in the medial part of the ventral horn throughout the spinal cord. A few crossing fibres were noted.

The lesion in the region of the nucleus reticularis medius also destroyed some ascending fibres passing by way of the f.l.m., viz., vestibulomesencephalic fibres which could be traced via the dorsomedial part of the f.l.m. to the nuclei III and IV. A few crossed vestibulomesencephalic fibres were also demonstrated to these nuclei. In addition a bilateral projection to the nucleus VI has been found.

In figure 45 the results in the turtle Testudo hermanni following a unilateral lesion of the f.l.m. at the level of the nucleus abducens are illustrated. The lesion interrupted ascending as well as descending components of the f.l.m. No involvement of the f.l.m. on the contralateral side was noted. The origin of the interrupted fibres was verified by studying the distinct, though not yet maximal retrograde cell changes. Chromatolysis was noted in the nucleus interstitialis of the f.l.m., in the nuclei reticulares isthmi, - superior and - medius, in all of these nuclei only ipsilateral to the side of the lesion. In addition a few cells in both nuclei vestibulares ventrolaterales showed chromatolysis.

Ascending degeneration could be traced, mainly ipsilateral, to the

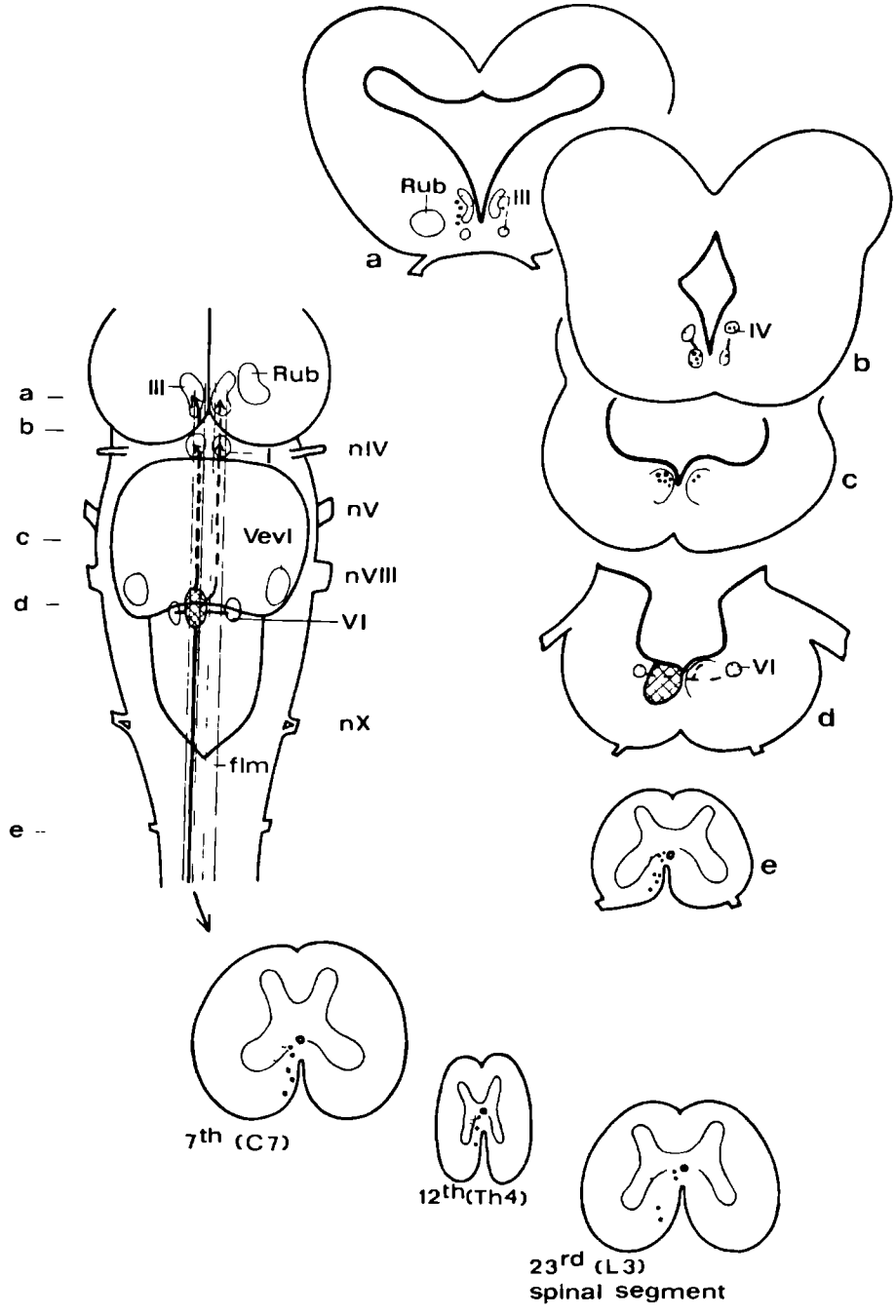


Fig. 45: A diagram and a series of transverse sections presenting the distribution of ascending and descending fibre degeneration following a unilateral lesion in the f.l.m. at the level of the nucleus abducens in Testudo hermanni. For symbols cf. fig. 40.

mesencephalon, particularly to the nuclei IV and III, in which terminal degeneration was noted in Fink-Heimer preparations. Rostral to the level of the nucleus III the small bundle of ascending degenerating fibres fades out in the vicinity of the nucleus interstitialis of the f.l.m. A few fibres could be traced to the area of the nucleus of the posterior commissure.

At the level of the lesion, bilateral degeneration could be followed to the nucleus VI in which terminal degeneration could be demonstrated in Fink-Heimer preparations.

Descending degenerating fibres could be traced, only ipsilateral, to the spinal cord as far caudal as the lumbar intumescence. It should be emphasized once more that it is very difficult to trace these relatively few fibres through the spinal cord. The fibres in question terminate in the medial part of the ventral horn of the spinal gray.

Finally, the results of a lesion in Python in the vestibular area, involving also the f.l.m. unilaterally, will be briefly dealt with. Retrograde cell changes were found in the nucleus interstitialis of the f.l.m. and in three reticular nuclei: the nuclei reticulares isthmi (bilaterally), - superior and - medius. The ascending and descending degenerating fibres demonstrated were comparable to those described for the lizard and the turtle. The descending fibre degeneration consists of a compact, dorsal and a more diffusely arranged ventral component. The former probably represents the interstitiospinal tract and the latter fibres probably are reticulospinal fibres arising in the nuclei reticulares isthmi, - superior and - medius.

Discussion:

The experiments discussed above clearly demonstrate that the components of the f.l.m. described in mammals (Busch, '61; Carpenter and Hanna, '62), viz., vestibulomesencephalic, interstitiospinal and reticulospinal fibres are also present in reptiles. Comparison with the detailed studies of Busch ('61, cat) reveals that the relative position of the constituent components of the f.l.m. in reptiles is quite similar to that in the cat. The presence of a vestibulospinal

tract passing via the f.l.m. could not be confirmed, however.

The ascending components as demonstrated in the turtle are basically comparable to the projection found in the cat by Carpenter and Hanna ('62) who following a similar lesion as the one in turtle (fig. 45) demonstrated a projection to the nuclei VI, IV and III, to the nucleus interstitialis of Cajal, the nucleus of the posterior commissure and to the vicinity of the nucleus of Darkschewitsch.

A vestibulomesencephalic projection by way of the f.l.m. has also been demonstrated in the frog Rana catesbeiana (Fuller and Ebbesson, '73; Fuller, '74). An analysis of Häggqvist material in the frog (Nieuwenhuys and Opdam, '76) showed as descending components of the f.l.m. interstitiospinal and reticulospinal fibres. It may be stated that the f.l.m. represents an old fibre system, which throughout the vertebrates mentioned is composed of the same fibre systems.

Finally, it should be mentioned that no selective lesions could be placed in either the nucleus reticularis inferior or the nucleus raphes inferior. However, studies with retrograde techniques (chapter V) have revealed that this part of the reticular formation projects caudally via the lateral funiculus, rather than by way of the f.l.m.

VII GENERAL DISCUSSION

In this study the descending pathways from the brain stem to the spinal cord have been investigated in the reptiles Testudo hermanni, a turtle, Tupinambis nigropunctatus, a lizard, and Python reticulatus, a snake.

A careful analysis of these fibre systems in normal material (Häggqvist) provided the necessary basis for experimental investigations, which were carried out with the help of retrograde as well as anterograde techniques. The retrograde techniques have been employed to study the origin , whereas with anterograde degeneration techniques more particularly the course and mode of termination of the supraspinal descending pathways have been studied. In figure 46 the results obtained are illustrated in a diagrammatic way.

In the lizard Tupinambis nigropunctatus and in the turtle Testudo hermanni the following pathways have been demonstrated, each passing as far as the lumbar intumescence:

1) a crossed rubrospinal tract descending along the lateral wall of the brain stem and passing via the most dorsal part of the funiculus lateralis; this pathway terminates in the so-called intermediate zone of the spinal gray matter, i.e. the area between the dorsal and the ventral horn;

2) a predominantly ipsilateral interstitiospinal tract, which in the spinal cord occupies the more dorsal part of the ventral funiculus;

3) a (lateral) vestibulospinal tract projecting bilaterally to the spinal cord, the smaller contralateral projection via fibres which cross in the most caudal part of the brain stem; this tract probably arises exclusively in the nucleus vestibularis ventrolateralis. No medial vestibulospinal tract, passing by way of the f.l.m. as suggested by the Häggqvist material and present in mammals, could be demonstrated;

4) two reticulospinal pathways, viz., one arising in the rostral part of the magnocellular reticular formation, i.e. the nuclei reticulares isthmi, - superior and - medius, the other originating in the nucleus reticularis inferior and in the nucleus raphes inferior. The first contingent passes by way of the f.l.m. in the caudal brain stem and

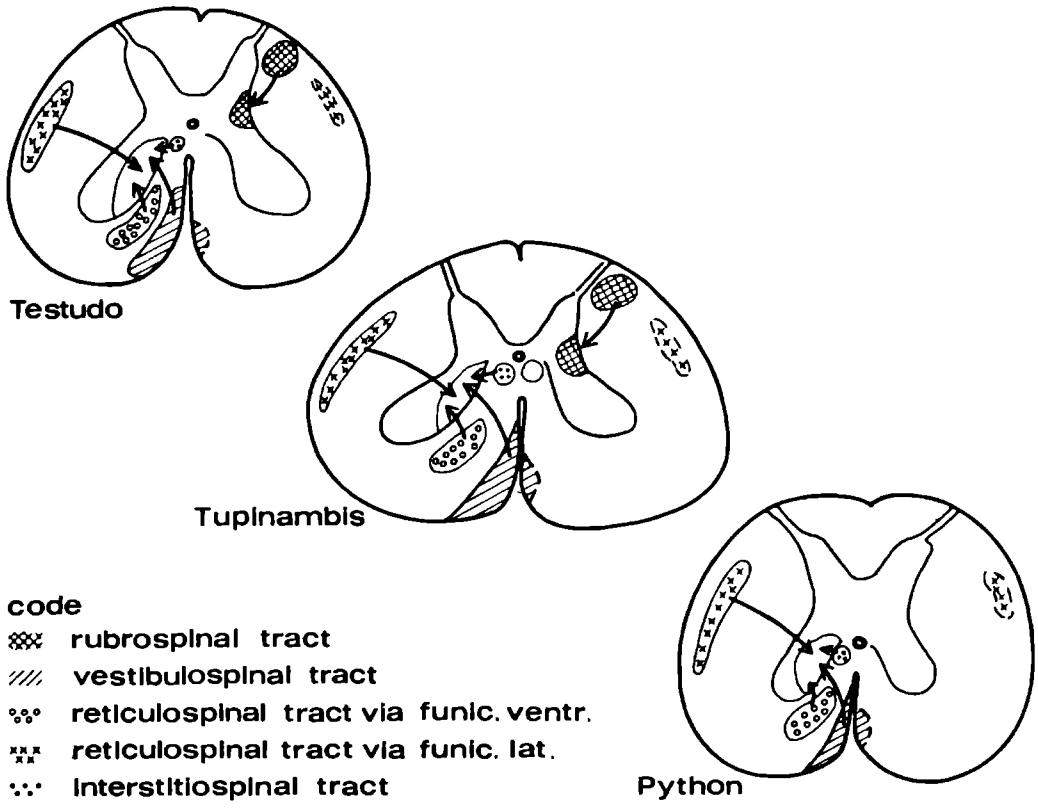


Fig. 46: Diagram summarizing the observations made in this study, represented in approximately comparable transverse sections, viz., the cervical intumescence in Testudo and Tupinambis, and the 10th spinal segment in Python.

further caudalward as a diffuse system in the ventral funiculus, whereas the second pathway is situated in the ventral part of the lateral funiculus.

The interstitiospinal, vestibulospinal and reticulospinal tracts all terminate in the medial part of the ventral horn.

No tectospinal pathway has been found. However, an extensive projection from the tectum mesencephali upon the magnocellular reticular formation has been demonstrated, which via reticulospinal fibres provides a way for tectal influences upon the spinal motor centres.

In the snake Python reticulatus apart from quantitative variations

in the reticulospinal (better developed than in the turtle and lizard) and in the vestibulospinal (less developed than in the other reptiles studied) tracts, the most remarkable difference demonstrated is the apparent absence of a rubrospinal tract in Python. Following high cervical hemicordotomies 1) no retrograde cell changes were found in the medial part of the tegmentum mesencephali, and 2) no anterograde degeneration could be traced comparable to the rubrospinal tract in Testudo hermanni and in Tupinambis nigropunctatus.

Two sites of termination for descending supraspinal fibres systems have been demonstrated, viz., the intermediate zone for the rubrospinal tract, whereas intersitiospinal, reticulospinal and vestibulospinal fibres terminate in the medial part of the ventral horn. Almost no termination of descending fibre systems could be demonstrated in the lateral column of motoneurons innervating the extremity musculature, a finding corresponding to what is known in mammals (Kuypers, '64; Brodal, '69). Direct terminations to this column are present in increasing numbers in the monkey, chimpanzee and man (Kuypers, '64). This increase is related to the development of individual finger movements. This relation is further exemplified by the presence of such terminations in the raccoon, a non-primate with very detailed finger movements (Petras, '68, '69; Wirth et al,, '74). In the class of reptiles no species able to exert individual finger movements are found. For this reason the absence of degeneration in the lateral column of motoneurons is not surprising.

As regards course and site of termination of the descending pathways demonstrated in reptiles a classification can be made as advocated in mammals by Kuypers (Kuypers et al., '62; Kuypers, '64; Lawrence and Kuypers, '68a, b) into lateral and (ventro)medial systems. The lateral system consists of fibres occupying a lateral position in the lower brain stem, descending into the lateral funiculus of the spinal cord and terminating in lateral and dorsal parts of the intermediate zone, whereas the medial system occupies a ventral and medial position in the lower brain stem and descends in the spinal cord via the ventral

funiculus and the ventral part of the lateral funiculus. The medial system terminates in the mediodorsal parts of the ventral horn and the adjacent parts of the intermediate zone.

The application of such a classification of the descending pathways is particularly interesting for the reptiles studied, since the medial system of descending fibre tracts (interstitiospinal, reticulospinal and vestibulospinal pathways) is functionally related to postural activities and progression, and constitutes a basic system by which the brain exerts control over movements (Lawrence and Kuypers, '68b). The lateral system of brain stem pathways (the rubrospinal tract), at least in regard to the extremities, superimposes upon the general motor control mentioned above the capacity for the independent use of the extremities, particularly of the hand. In mammals the corticospinal connexions mediate a control similar to that of the lateral brain stem system, but superimposes in addition speed and agility upon these subcortical mechanisms. Moreover, the corticospinal tract provides the capacity for fractionation of movements as exemplified by individual finger movements (Lawrence and Kuypers, '68a, b).

The classification of the fibre systems descending to the spinal cord in mammals just reviewed renders it likely that in Python the absence of a rubrospinal pathway is correlated to the absence of limbs. In Testudo hermanni and Tupinambis nigropunctatus, however, the rubrospinal tract demonstrated, shows all characteristics of a lateral system, viz., 1) a lateral position in the lower brain stem and spinal cord, and 2) terminating in an area (the intermediate zone) comparable to the dorsal and lateral parts of the intermediate zone in mammals. That this tract is related to the (more or less independent) use of the extremities is also suggested by the finding that in reptiles the rubrospinal tract terminates most extensively in the cervical and lumbar intumescences.

In reptiles the vast majority of the fibres descending from the brain to the spinal cord, viz., interstitiospinal, reticulospinal and vestibulospinal fibres, can be classified together as a medial system. All of these pathways occupy a ventral and medial position in the lower

brain stem, descend in the ventral funiculus or in the ventral part of the lateral funiculus, and terminate in an area of the spinal gray comparable to the ventral and medial parts of the intermediate zone in mammals.

Finally, some general notes will be made on the pattern of descending pathways to the spinal cord in terrestrial vertebrates. In figure 47 a schematic representation is given of experimental data concerning these pathways in amphibians (toad and bullfrog), in reptiles (the tegu lizard), in the pigeon and in the cat (Staal, '61; Nyberg-Hansen, '66, '69). In this diagram comparable fibre systems and their area of termination are indicated with the same code.

A vestibulospinal tract, projecting bilaterally to the spinal cord, has experimentally been demonstrated in the toad (Corvaja and Grofová, '72; Corvaja et al., '73) and in the bullfrog (Fuller, '74). In the toad (Corvaja and Grofová, '72) two other pathways have been shown. Following a high hemisection of the spinal cord these authors noted a dorsolateral tract, terminating in an area between the dorsal and the ventral horn, and a ventrolateral pathway, ending in the ventral horn. The dorsolateral tract could possibly represent a rubrospinal tract, as is further suggested by a vestibular lesion made by these authors, extending to the ventrolateral wall of the brain stem. Following this lesion a tract of degenerating fibres could be traced comparable to the rubrospinal tract demonstrated in reptiles. The origin of the ventrolateral pathway is still unknown; however, it seems likely that this pathway consists of reticulospinal fibres. The presence of reticulospinal fibres descending via the funiculus ventralis has been demonstrated by Nieuwenhuys and Opdam ('76).

In the pigeon a rubrospinal tract has been experimentally demonstrated by Zecha ('61) and van den Akker ('69, '70). This tract terminates in area 4 of van den Akker ('70), which corresponds to the intermediate zone in the reptilian spinal gray matter. Following a high hemisection of the spinal cord (van den Akker, '69) in addition to the rubrospinal tract a large ventral descending bundle has been

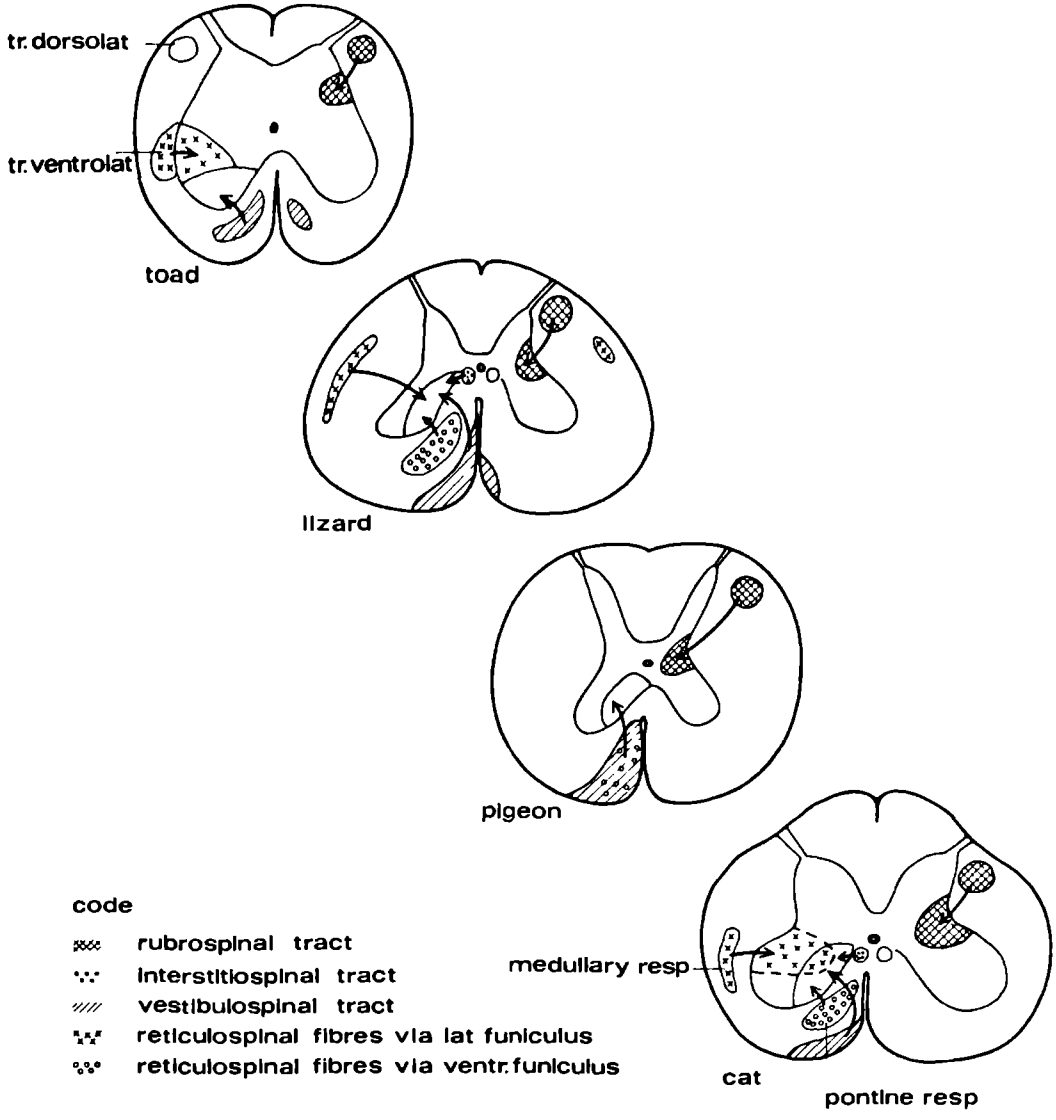


Fig. 47: Diagram summarizing experimental data concerning descending fibre systems from the brain stem to the spinal cord in amphibians (based on Corvaja and Grofová, '72), in the tegu lizard (the present study), in the pigeon (after van den Akker, '69, '70) and in the cat (redrawn from Nyberg-Hansen, '66). Comparable fibre systems and their area of termination are indicated with the same code in sections through the cervical intumescence.

shown in the ventral funiculus. This bundle consists of vestibulospinal (Groebbels, '27; Marchi technique) and of reticulospinal fibres (Janzik and Glees, '67).

Zecha ('62) also traced degenerating fibres originating from caudal forebrain regions into the posterolateral funiculus, but a true pyramidal system, bringing motor activity under the direct control of the cerebral cortex occurs only in mammals (Nieuwenhuys, '64), and even in mammals large variations have been observed. In the opossum (Martin and Fisher, '68) and in certain other lower mammalian forms (e.g. the rat: Brown, '71) a corticospinal tract descends via the dorsal funiculus and terminates in a region of the dorsal horn adjacent to the substantia gelatinosa. It is reportedly concerned more with the modulation of incoming afferent information, than with motor control (Brown, '71). In the opossum the corticospinal tract extends only to thoracic levels.

It has been suggested that where a functional corticospinal system is impaired or lacking the rubrospinal system is capable of motor control (Massion, '67). In the opossum the rubrospinal tract extends, in contrast to the corticospinal tract, the entire length of the spinal cord (Martin and Dom, '70a). The latter authors suggest that the rubrospinal tract plays an important role in the suprasegmental control over lower motor neuron activity. The motor area of the neocortex does not directly influence lower motor neuron activity within the lumbosacral cord, but is potentially capable of doing so indirectly by way of its projection to the red nucleus (Martin, '69b).

It has recently been demonstrated that in Tupinambis the medial part of the tegmentum mesencephali receives a projection from the dorsolateral part of the ventral striatum (Hoogland, '75). This projection provides a pathway by which the telencephalon might influence the spinal cord. Apart from the above projection the ventral striatum in Tupinambis projects profusely to the lateral part of the tegmentum mesencephali.

Surveying the results presented in figure 47 there appear to exist remarkable similarities in the descending pathways from the brain

stem to the spinal cord. In all of the groups depicted rubrospinal, reticulospinal and vestibulospinal tracts have been demonstrated, which terminate in comparable areas of the spinal gray matter.

Hence, throughout terrestrial vertebrates a fundamental pattern of organization in the descending fibre systems from the brain stem to the spinal cord is found. In reptiles a rather high degree of development is reached which is directly comparable to the condition in mammals.

VIII SUMMARY

In the present study the pathways descending from the brain stem to the spinal cord have been investigated in the reptiles Testudo hermanni, Tupinambis nigropunctatus and Python reticulatus. These reptiles, using highly different types of progression have been selected, because fundamental variations in the organization of the central motor apparatus are to be expected.

As a preliminary step an analysis of normal material has been made, in particular of series stained according to Häggqvist, This analysis suggested that in reptiles various fibre systems descend to the spinal cord, viz., interstitiospinal, reticulospinal, vestibulospinal and rubrospinal tracts.

For the experimental verification of the fibre systems recognized in the Häggqvist material various techniques have been used. The origin of the descending pathways has been demonstrated by recording the occurrence of retrograde cell changes following hemicordotomies and by searching for labeled cells following injection into the spinal cord of the enzyme horseradish peroxidase. Their course and their termination have been studied by tracing the ensuing fibre degeneration with anterograde techniques, following appropriate lesions in the brain stem.

In the three reptiles studied the presence of interstitiospinal, vestibulospinal and reticulospinal pathways has been demonstrated. A crossed rubrospinal tract has been shown in the turtle and lizard, but could not be demonstrated in Python. The presence of a tectospinal pathway of any importance could not be shown. However, the tectum mesencephali has been found to project profusely to the brain stem reticular formation. The rhombencephalic reticular formation comprises a nucleus raphes superior, a nucleus raphes inferior and nuclei reticulares isthmi, - superior, - medius and - inferior. All of these centres, except for the nucleus raphes superior send fibres to the spinal cord: the nucleus raphes inferior and the nucleus reticularis inferior by way of the lateral funiculus, the nuclei reticulares isthmi, - superior and - medius via the ventral funiculus.

The interstitiospinal trect projects predominantly to the ipsilateral side of the spinal cord. The vestibulospinal projection, arising from the large-celled nucleus vestibularis ventrolateralis, comprises a large uncrossed tract and a small decussating component.

The rubrospinal pathway terminates in a particular site of the spinal gray, i.e. the intermediate zone, whereas the interstitiospinal, reticulospinal and vestibulospinal tracts all terminate in the medial part of the ventral horn.

It appeared that the classification of descending pathways as advocated in mammals by Kuypers into lateral and medial systems can be readily applied to reptiles. The lateral system terminates in the dorsal and lateral parts of the intermediate zone, the medial system predominantly in the dorsomedial part of the ventral horn. This classification renders it likely that the absence of a lateral focus of termination as well as the absence of a rubrospinal tract in Python, is correlated to the absence of limbs.

A comparison of experimental data concerning the systems descending from the brain stem to the spinal cord in amphibians, reptiles, birds and mammals suggests that these systems with regard to origin,course and termination have a basic pattern in common.

IX. SAMENVATTING.

Een oriënterend onderzoek van normaal vezelmateriaal (Häggqvist) bij de schildpad Testudo hermanni, de hagedis Tupinambis nigropunctatus en de slang Python reticulatus wekt de indruk, dat de vezelsystemen die bij deze reptielen vanuit de hersenstam naar het ruggemerg afdalen, wat hun oorsprong en verloop betreft, sterk op die van zoogdieren lijken. Deze systemen zijn: 1) de fasciculus longitudinalis medialis (f.l.m.) die bijzonder sterk ontwikkeld is en vooral reticulospinale vezels bevat; 2) de fasciculus predorsalis, een vanuit het tectum mesencephali afdalend en kruisend systeem; 3) de verbinding van de grootcellige nucleus vestibularis ventrolateralis met het ruggemerg, en 4) de tractus rubrospinalis.

Gezien de opvallende verschillen bij de drie genoemde reptielen in de organisatie van het spinale motorische apparaat (aanwezigheid en uitbreiding van mediale en laterale kolommen van motorische neuronen in de voorhoorn) werd nagegaan of bij deze reptielen ook de vanuit de hersenstam naar het ruggemerg afdalende vezelsystemen in omvang en uitbreiding verschillen.

De techniek om experimenteel te verifiëren welke centra in de hersenstam naar het ruggemerg projekteren, is het analyseren van de na ruggemergsdoorsnijdingen optredende retrograde celveranderingen. De kriteria hiervoor zijn: tigrolyse, zwelling van het cellichaam en het zich naar perifeer verplaatsen van de celkern. Uit halfzijdige ruggemergsdoorsnijdingen bij Testudo, Python en Tupinambis op cervicaal en thoracaal niveau blijkt dat in de volgende celarealen de aangeduide celveranderingen optreden: 1) de nucleus interstitialis van de f.l.m. (bilateraal); 2) de nucleus ruber (contralateraal), echter alleen bij Testudo en Tupinambis; 3) de grootcellige nucleus vestibularis ventrolateralis (bilateraal) en 4) de reticulaire formatie.

De reticulaire formatie bij reptielen toont een duidelijke gelijkenis met die bij zoogdieren. Evenals bij deze (Brodal, '57) is een onderverdeling te maken in drie longitudinale zones: 1) een mediane zone, waarin zich twee celkondensaties bevinden, nl. de nucleus raphes inferior en - superior; 2) een mediale zone, onderverdeeld

in de magnocellulaire nuclei reticulares inferior, -medius, -superior en -isthmi; 3) een laterale, parvocellulaire zone. Retrograde celveranderingen werden gevonden in de nuclei raphes inferior, in de nuclei reticulares inferior (bilateraal), -medius, -superior en -isthmi; in de laatste drie kernen voornl. ipsilateraal.

Opmerkelijk is dat er na ruggemergsdoorsnijdingen lager dan hoogthoracaal geen retrograde celveranderingen werden waargenomen. Het lijkt waarschijnlijk dat de aanwezigheid van collateralen proximaal van de doorsnijding van de axonen de cellen voor degeneratie behoedt. Teneinde toch via retrograde weg na te gaan welke celgebieden in de hersenstam naar de kaudale delen van het ruggemerg projekteren, met name naar de lumbale intumescentie, werd het enzym horseradish peroxidase (mierikswortel peroxidase) ingespoten in de lumbale intumescentie van Testudo en Tupinambis. Dit enzym wordt door axoneindigingen opgenomen en retrograad naar het cellichaam getransporteerd. Met behulp van deze techniek werd aangetoond dat alle bovengenoemde descenderende verbindingen vanuit de hersenstam ook de kaudale delen van het ruggemerg bereiken.

Het verloop en de eindigingswijze van de naar het ruggemerg descenderende verbindingen werd nagegaan door het bestuderen van anterograde vezeldegeneratie met behulp van de Nauta-Gygax en Fink-Heimer technieken, na gerichte lesies in de hersenstam. Aangetoond werd dat de tractus interstitiospinalis, de tractus vestibulospinalis en de reticulospinale vezels, die uit de nuclei reticulares medius, -superior en -isthmi ontspringen via de funiculus ventralis verlopen, terwijl de tractus rubrospinalis en de reticulospinale vezels vanuit de nucleus reticularis inferior en nucleus raphes inferior via de laterale funiculus afdalen.

De rubrospinale baan eindigt in het laterale deel van het intermediaire gebied in het spinale grijs, terwijl de overige systemen eindigen in het mediale deel van de voorhoorn.

De aanwezigheid van een rubrospinale baan kon niet worden aangetoond bij de Python. Het lijkt aannemelijk dat de afwezigheid van een tractus rubrospinalis bij deze species gekorreleerd is met de afwezigheid

van extremiteiten.

Een vergelijking vanexperimenteel-anatomische gegevens bij amfibiëen, reptielen, de duif en zoogdieren bracht aan het licht dat de descenderende verbindingen vanuit de hersenstam naar het ruggemerg bij deze vertebraten in grote lijnen vergelijkbaar zijn.

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Curriculum vitae

H.J. ten Donkelaar werd geboren op 16 augustus 1946 te Hengelo (O). Na het afleggen van het staatsexamen HBS-B in 1965 begon hij zijn studie in de geneeskunde aan de Universiteit van Nijmegen in hetzelfde jaar. In oktober 1970 werd het doktoraalexamen en in juni 1974 het artsexamen afgelegd. Vanaf maart 1972 is hij in dienst van het Laboratorium voor Anatomie en Embryologie van de Katholieke Universiteit te Nijmegen.

STELLINGEN

I

Ten onrechte wordt door het Boulder Committee gesteld dat de subventriculaire (of subependymale) laag in alle delen van het zich ontwikkelende centrale zenuwstelsel voorkomt.

The Boulder Committee (1970): Anat. Rec., 166: 257-262

II

De verbindingen van het cerebellum en van de basale ganglia tonen in hun organisatie een duidelijke overeenkomst.

Evarts en Thach (1969): Ann. Rev. Physiol., 31: 451-498

Kemp en Powell (1971): Phil. Trans. R. Soc. Lond. B., 262: 441-457

III

De basale ganglia funktioneren primair bij het voortbrengen van langzame ('ramp')bewegingen, terwijl het cerebellum snelle ('ballistic') bewegingen preprogrammeert en in gang zet.

Kornhuber (1971): Kybernetik, 8: 157-162

IV

Zinvol experimenteel-hodologisch onderzoek kan slechts op basis van grondige kennis van normaal materiaal plaatsvinden.

V

De hypothese (Yoon en Harper, 1973; Bauer e.a., 1974; Richardson e.a., 1974), dat hyaliene membranenziekte in een lagere frequentie zou voorkomen bij kinderen geboren na het langdurig (meer dan 24 uur) gebroken zijn van de vliezen, is onjuist (Jones e.a., 1975).

Yoon en Harper (1973): Pediatrics, 52: 161-168

Bauer e.a. (1974): Pediatrics, 53: 7-12

Richardson e.a. (1974): Am. J. Obstet. Gynecol., 118: 115-118

Jones e.a. (1975): New Engl. J. Med., 292: 1253-1257

VI

Enkele veelgebruikte antikonvulsiva hebben een teratogene werking.

Loughnan e.a. (1973): Lancet, 1: 70-72

Lowe (1973): Lancet, 1: 9-10

Wilson (1973): Teratology, 7: 3-15

VII

Formaline-infiltratie van de ductus arteriosus is een effectieve palliatieve techniek voor de behandeling van bepaalde kongenitale hartafwijkingen.

Rudolph e.a. (1975): New Engl. J. Med., 292: 1263-1268

VIII

Bij het vinden van atypische epitheelcellen in het cervix-uitstrijkje dient men bedacht te zijn op maligne ontaardingen van de tuba uterina.

Benson (1974): Acta cytol. (Philad.), 18: 429

Pascu e.a. (1975): Dtsch. Med. Wschr., 100: 1476-1477

IX

Het schrijven van een proefschrift is niet meer, maar ook niet minder dan het begin van een mogelijke wetenschappelijke karrière.

3 oktober 1975

H.J. ten Donkelaar